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The Journal of Allergy

VOL. 11 MAY, 1940 NO. 4

Original Articles

AN INQUIRY INTO REAGINS IN CONVALESCENT SERUM INDICATING ITS INHIBITING EFFECT

I. HARRISON TUMPEER, M.D., AND ELI RUBENS, M.D.
CHICAGO, ILL.

CONVALESCENT serum for prevention and treatment of various diseases, in children particularly, is attaining steadily greater usefulness as its effectiveness is realized and facilities for its collection and distribution are provided. It is logical for the pediatrician specializing in allergy to ponder the possibilities of allergic reactions from this serum derived from human beings. It is reasonable to expect that reagins are present in the serum in view of the relatively large percentage of allergic individuals in the general population. By the law of averages, many convalescent serum pools should contain these reagins and, therefore, should produce massive passive transfer upon injection. Conversely, by the same law of averages, the patient requiring convalescent serum may be allergic and, therefore, may possess reagins specific for the food factors in the donor's recent dietary, resulting in a picture resembling allergic reactions from transfusion. In the midst of these speculations, the interested clinician begins to encounter an occasional patient who develops an eruption, not typically urticarial, following the administration of convalescent serum.

This phenomenon naturally conjures up the peculiar allergic reactions occurring with blood transfusions. Although there are significant differences in the two situations, including dilution, pooling per se, filtration, preservation and age of serum, it will illuminate the problem under investigation if reference is made to the more simple serologic reactions produced by blood transfusions. In this connection must be mentioned the classical case of Ramirez,[1] reported in 1919, in which a recipient of a blood transfusion from a donor sensitive to horse dander developed asthma two weeks later upon contact with horses. Another example of reagin transfer is the case of Holder and Diefenbach[2] in which urticaria

From the Children's Allergy Section, the Sarah Morris Hospital for Children, and the Samuel Deutsch Convalescent Serum Center of the Michael Reese Hospital, Chicago.

Read before the Annual Meeting of the American Society for the Study of Allergy, St. Louis, Mo., May 15, 1939.

to strawberries was produced, a tendency which persisted for four months after the transfusion. This is tantamount to the production of massive passive transfer in which reagins are transmitted to a non-allergic person rendering him sensitive like the donor as long as the reagins persist in the serum in adequate quantities. Active transmission of urticaria was the subject of an interesting report by Tedstrom.[3] The donor admitted having hives from strawberries at the time of transfusion. Significant was the fact that, when the same donor was used two weeks later, free from urticaria, no eruption occurred. The immediate type of allergic reaction on transfusion is ordinarily due to the transference of allergens from the donor to a sensitive recipient possessing reagins specific for the allergens. An example of this type is the milk-sensitive patient of Duke and Stofer[4] who reacted immediately to the blood of a donor who had fortified himself with milk before he was bled. Littlefield[5] described a case of marked urticaria, cough, and gastrointestinal symptoms in a woman subject to hives from eggs whose donor husband admitted having an eggnog before transfusion. Stewart and Bates[6] had a similar experience in a woman sensitive to shellfish whose donor had partaken of this delicacy the night before—incidentally illustrating the fact that food factors may remain in the circulation as allergens in clinically adequate quantities for a much longer period than the conventional fast after supper. It is also obvious that reactions from the donor depend, too, on the degree of sensitivity of the recipient or concentration of reagins in his serum. In the same etiological category is the case of a woman who developed hives during the course of a transfusion. She was known to react in this manner to gin only, which she had not touched for fifteen years. The donor admitted having taken one drink the morning before the transfusion.[7] At times fatal reactions to transfusion have been reported on an allergic basis. This is illustrated in the case of Hancock's patient[8] with cerebral edema and bloody spinal fluid and in a case of one of us (I. H. T.) of a child with coincident Arthus phenomenon.[9, 10]

STUDY A

Methods.—In the first attempt to test typical specimens of convalescent serum for reagins, the following types were used:

20	Erysipelas convalescent	serum pool of	7 specimens
30	Normal	serum pool of	27 specimens
11	Poliomyelitis convalescent	serum pool of	23 specimens
13	Poliomyelitis convalescent	serum pool of	41 specimens
17	Poliomyelitis convalescent	serum pool of	53 specimens

The recipients for passive transfer were thirty-one mothers of allergic children in attendance at the Children's Allergy Section, Mandel Clinic, of Michael Reese Hospital. The routine procedure consisted of transferring 0.1 c.c. of serum to each of twenty sites on each subject. After

an interval of one week these areas and untreated controls on the same arms were injected intracutaneously with concentrated extracts of twenty common allergens to determine whether or not reagins to these common allergens were present in the transferred sites and therefore in the original sera employed.

Results.—The results were vague and inconsistent. For instance, 5 of the 31 mothers reacted within five minutes with pseudopods upon the injection of the serum itself: 1 for the poliomyelitis pool of 53 bloods; 2 for the erysipelas pool of 7 bloods; and 2 for the normal pool of 27 bloods. The two other poliomyelitis pools of 23 and 41 specimens, respectively, produced no immediate reactions. When the allergens were subsequently applied, reactions were numerous both on control and transfer and seemingly inconsistent because the same serum failed to yield the same reactions on different patients. At times it was suggestive that the control sites reacted more strongly than the transferred areas, seemingly implying that the transferred serum might be inhibiting the response as compared with the recipient's own control.

It was decided that mothers of allergic children were too allergic, themselves, or too dermographic, to be trustworthy for this type of passive transfer experiment to detect reagins in convalescent serum.

STUDY B

Methods.—To obtain what we hoped would be a more average section of the population for transfer studies, we availed ourselves of the opportunity of employing the mothers of premature babies who were bringing their children for the routine immunologic round-up conducted by the premature baby follow-up division. The following sera were used:

10	Chicken pox	convalescent serum	pool of	4 specimens
23	Erysipelas	convalescent serum	pool of	9 specimens
27	Poliomyelitis	convalescent serum	pool of	15 specimens
D46	Poliomyelitis	convalescent serum	pool of	18 specimens
294	Scarlet fever	convalescent serum	pool of	38 specimens
296	Scarlet fever	convalescent serum	pool of	38 specimens

Each lot was transferred to 20 sites in each of five recipients. Some of these reacted to the injection with pseudopods and wheals as in the first group. To obtain data concerning the immediate reactivity of each of the sera, each subject was also inoculated with each of the five remaining sera aside from the serum used for her 20 sites. This permitted a study of each serum on 30 persons. To determine the reaction to fresh, unfiltered, unpreserved, unpooled serum, one woman of each group of five was bled. After a negative Wassermann test, this serum was transferred to each woman of the group of five, including the donor herself. In addition to these controls, tricresol 0.3 per cent in ether 0.3 per cent, and merthiolate, 1:10,000, were applied to each subject because these

preservatives were present in the convalescent serum itself. Tests for reagins were made with the same allergens as in Study A.

Results.—Immediate responses to injections of pooled convalescent serum were numerous and were practically the same for each of the six sera. This indicates that there may be some irritating factor in collections of human serum after pooling, passing through Berkefeld filters, and treating with preservatives. Reactions to fresh serum are definitely less common, but even here there are peculiar pictures. Two of the women from whom blood was drawn reacted to their own sera, and reactions occurred in 5 of the 6 sera on 10 of 30 subjects. There were practically no reactions to the preservatives themselves (Table I).

TABLE I (STUDY B)

REACTIONS OF EXPERIMENTAL RECIPIENTS TO VARIOUS CONTROLS

CONTROL USED	REACTIONS				
	0	+	++	+++	++++
Preservative					
Tricresol 0.3%	29	1			
Merthiolate 1:10,000	26	1	3		
Serum					
C10	7	4	16	3	
E23	6	2	19	3	
D46	7	5	15	3	
P27	5	3	17	4	
S294	7	5	15	3	
S296	7	6	13	3	1 (pseudopods)
Fresh Single Serum Group Representative on Five Recipients Including Donor					
Ar.	4	1			
Ch.	1	1	2	1 (her own)	
Cr.	3		1	1 (her own)	
Li.	4			1	
Na.	3		2		
Su.	5				

Despite the fact that this was a nonselected group, 15 of the 30 women were from allergic families. Five had allergic children, and 10 were themselves allergic, agreeing generally with Service's[11] recent survey in Colorado Springs where he found 22.6 per cent of the population allergic.

Three of the 6 sera gave reactions to 10 allergens in 9 persons, 13 reactions in all. None of the transfer reactions were more than moderately positive, and no serum reacted more than once to the same allergen (Table II).

It is striking that the results with this supposedly more average group of subjects were about the same as those with the group of mothers of allergic children, namely, a frequency of varying response to serum directly and an irregularity of response to allergens in control and transferred areas, indicating that transfer of reagins had not occurred to any demonstrable extent.

TABLE II (STUDY B)

POSITIVE FEACTIONS TO 20 COMMON ALLERGENS IN 6 POOLED SERA IN STUDY B

ALLERGEN	C10 (4)*	P27 (15)	S294 (38)	PD46 (18)	E23 (9)	S296 (38)
			Left Arm			
1. Cottonseed						
2. Kapok			++			
3. Wool						
4. Silk			++			
5. Feathers	++	++				
6. Cat hair						
7. Cow hair						
8. Dog hair						
9. Dust			++			
10. Glue						
			Right Arm			
1. Flaxseed						
2. Orris root		++				
3. Horse hair	++	++				
4. Milk						
5. Wheat		++				
6. Egg white		++				
7. Mustard						
8. Almond		++	++			
9. Grass mixture 1:50		++				
10. Weed mixture 1:50						

*Number of sera in pool.

Again was noted the interesting phenomenon of greater response to an allergen on an untreated than on a transferred skin site, which was noted in the first group.

If any appreciable concentration of reagin had been originally transferred, it might be expected that one of the thirty might betray the Walzer type of reaction when she came for final testing the following week at an hour shortly after breakfast. Anticipating such an occurrence, each subject was questioned concerning the contents of her breakfast in order to evaluate the results. There was a wide variety of answers from nothing at all to rather elaborate repasts. We entertained the thought that some woman might have eaten some food which would still be circulating in her blood when she came for testing and which might interact with her serum sites if the serum contained reagins for such common foods as milk or eggs, for instance. In none of the thirty persons was this phenomenon observed, although this was suspected when certain of the women reacted to the twenty original serum injections with pseudopods at each site within a few minutes. In the latter setup we felt that these women had eaten some food prior to testing, which was already circulating when the testing convalescent serum presumably containing reagins was originally administered, although the serum may have contained allergens, i.e., foods, for which the recipients had reagins inasmuch as ten of them knew they were allergic.

It could be concluded on the basis of the studies on these two groups that either the reagin content of pooled serum is too small to betray

itself by passive transfer studies or that something happens in the processing or mixing of sera to neutralize, inhibit, or "block" the activity of the reagins. The ineffective concentration might be on the basis of the dilution factor alone, but this did not seem reasonable if some extremely sensitive patient were included in a pool. It should be expected that serum from such persons would contain enough reagin to "break through" such dilution.

Clinical experience with convalescent serum confirms these serologic studies. It is the consensus of experience among serum stations that reactions are uncommon and danger absent. Thalhimer[12] stated that no allergic phenomena or reactions were noted after repeated injections of serum in the experience of two children's hospitals, with the exception of what he terms "a mild urticaria or a temperature rise not above one degree." Three-hour fasting donors were used. Hyland[13] felt that the question of reactions and sensitization following the use of this serum might be disregarded entirely because it is an homologous serum. He reported the administration of thousands of doses intravenously and intramuscularly in patients of all ages without reactions. Hardgrove[14] believed that the question of serum reactions could be almost disregarded because no serious reactions had been observed. Later Fox and Hardgrove[15] reported an incidence of 1 per cent of reactions. These were transitory rises in temperature, chills, and articular pains. Mild urticaria occurred occasionally within twenty-four hours, or as long as two or three weeks later.

A review of the reported reactions occurring after the administration of scarlet fever convalescent serum from the Samuel Deutsch Convalescent Serum Center of the Michael Reese Hospital, which was made with the cooperation of its director, Dr. S. O. Levinson, revealed interesting data along the same lines. There were reports of 36 reactions in 3,708 cases, slightly less than 1 per cent, and even less if numbers of injections were considered rather than individual cases. The reaction rate and interval of reactions closely approximated the report of Fox and Hardgrove. The reactions were mainly of a mild urticarial nature and occurred at the following intervals:

1st day, 1 reaction
3rd day, 1 reaction
4th day, 2 reactions
5th day, 2 reactions
6th day, 1 reaction
7th day, 3 reactions
9th day, 3 reactions (One of these was called serum-sickness)
10th day, 1 reaction
12th day, 1 reaction
16th day, 1 reaction
21st day, 2 reactions
Day not stated, 18 reactions

Eleven, or about one-third, of the reactions occurred in 3 lots of serum, 3 from one, 3 from another, and 5 from the third, from a total of 147 lots. In other words, 30 per cent of the reactions occurred from 2 per cent of the sera. Upon investigation it was found that one of the lots contained serum from a group of patients who had been given prophylactic diphtheria antitoxin because of a contact in the scarlet fever ward. The cases from the lot producing 5 reactions developed from five to sixteen days after treatment, and one of them developed asthma, as well as a rash, at the time. This demonstrates that reactions may occur under special circumstances, but that reactions are, nevertheless, uncommon and rarely severe.

In the regular course of events there should be as many allergic recipients with reagins in their blood ready to react with a transferred allergen present in convalescent serum, as there are allergic donors whose reagins are contained in the serum transferred. From the fact that the reactions are rarely immediate (in our series there was only one reaction within 24 hours), it would appear that allergens, particularly in the form of food factors, are either absent or neutralized in the pooled serum, or that they are further inhibited by the allergic recipient's serum, which seems paradoxical when considering allergic transfusion reactions. Even the three-hour fasting period practiced is not sufficient to exclude food allergens from the circulation, as attested to by the transfusion reaction described above, particularly in the case of Stewart and Bates in which a food eaten the night before provoked a reaction. The fact that most of the reactions are of the delayed type would speak for a massive passive transfer of reagins which only awaits favorable contact with the specific allergen to produce reactions. This type is comparable to Ramirez's patient who reacted with horses two weeks after transfusion with a horse-sensitive blood. In all this reasoning, the dilution factor has not been ignored. Yet we return to the proposition that somewhere high titer reaginic sera must encounter allergens and that the nature of the allergen, i.e., fish, nuts, or similar potent allergens, despite dilution, must produce interactions of clinical note. Furthermore, the fact that reagins are not demonstrated in a site to which only 0.1 c.c. of serum has been transferred cannot deny the possibility of a reaction when 200 to 2,000 times that amount of serum, i.e., 20 c.c. to 200 c.c., is given quite frequently in ordinary clinical practice, particularly when the serum is administered intravenously.

STUDY C

Methods.—Following the unsuccessful search for reagins in convalescent serum, which could justifiably be assumed to include serum from allergic persons, it was decided to prepare a "synthetic" mixture by adding serum from known highly sensitive ragweed hay fever patients

to convalescent serum. A scarlet fever convalescent serum, S322, prepared from 36 specimens, was used to dilute two ragweed reacting sera hereafter referred to as "serum No. 1" and "serum No. 2" from 1:10 to 1:1,000,000. Two nonallergic boys who did not react to 1:50 ragweed extract were inoculated with 0.1 c.c. of each undiluted ragweed reacting serum by the usual method of passive transfer and with serial dilutions of the same sera prepared in the S322 pooled serum. In addition, the S322 convalescent serum used for diluent was injected as a control. Three days later each area was tested with 1:50 ragweed extract.

Results.—There was no reaction to the convalescent serum control. J. S. reacted to both specimens of whole ragweed serum on first injection. M. C. gave a four-plus reaction with 1:50 ragweed extract on the site of undiluted ragweed serum. One of the areas gave marked itching. There were no reactions with any of the dilutions, even the 1:10 of ragweed serum mixed with pooled convalescent serum (Experiment 1). This was amazing because we knew from previous passive transfer experiments, including one in which we repeated this type of titration in a more elaborate series below, that the

EXPERIMENT 1 (STUDY C)

INHIBITION OF PASSIVE TRANSFER REACTION WHEN REAGINIC SERA ARE DILUTED WITH POOLS

RECIPIENT, M.C. RAGWEED SERA DILUTED IN S322. TEST EXTRACT, RAGWEED 1:50.

LEFT ARM		RIGHT ARM	
DILUTION OF SERUM NO. 1	REACTION	DILUTION OF SERUM NO. 2	REACTION
Undiluted	++++	Undiluted	++++ (itch)
1:10	0	1:10	0
1:100	0	1:100	0
1:1,000	0	1:1,000	0

No reactions to undiluted serum itself.

whole serum in the case of ragweed reaginic serum No. 1 would react to 1:5,000,000 ragweed extract on transfer. J. S., who reacted to the undiluted serum directly, reacted four-plus when ragweed extract 1:50 was superimposed on undiluted serum No. 1, and not at all to the dilutions of this serum in pooled sera. With serum No. 2 with ragweed extract 1:50 he reacted to the whole serum, the 1:10 dilution, and slightly to the 1:100. Paradoxically, this was the serum from the somewhat less sensitive hay fever patient, a finding which occurs in allergy to refute the assumption that such studies are strictly quantitative. The qualitative element is displayed in the fact that he reacted to both sera on the original inoculation (Experiment 2).

Ragweed pollen reagins are inhibited when a reaginic serum known to react on passive transfer to a 1:5,000,000 dilution of pollen extract

EXPERIMENT 2 (STUDY C)

PHENOMENON OF EXPERIMENT 1 OBTAINED IN ANOTHER SUBJECT

RECIPIENT, J.S. RAGWEED SERA DILUTED IN S322. TEST EXTRACT, RAGWEED 1:50.

LEFT ARM		RIGHT ARM	
DILUTION OF SERUM NO. 1	REACTION	DILUTION OF SERUM NO. 2	REACTION
Undiluted	++++	Undiluted	++++
1:10	0	1:10	++++
1:100	0	1:100	++
1:1,000	0	1:1,000	0

Whealing to both sera directly.

is itself diluted 1:10 in pooled convalescent serum and tested with 1:50 pollen extract. It would seem that the factors of pooling, filtration, and preservation interfered with or interacted in some colloidal manner with the known high concentration of reagins. Mere dilution did not seem to explain the phenomenon. This was confirmed in Study D. The results of the dilution experiments when carried out in pooled serum agree with clinical experience in which so few reactions occur, even when the serum is administered intravenously. These results give visible demonstration of the explanation of the rarity of reactions. We have evidence, therefore, that convalescent serum which might include reaginic serum No. 1, which reacts to ragweed extract as dilute as 1:50,000,000 on the patient herself and 1:5,000,000 on passive transfer, would give no test for ragweed reagins. This would account for our failures to detect reagins in Studies A and B.

STUDY D

Methods.—To determine whether or not the diluting medium was the significant factor, further dilutions of the known sera were prepared in physiologic solution of sodium chloride. To control the factors of Berkefeld filtration and preservation, dilutions were also prepared in a fresh pooled serum before these measures had been carried out and in the identical lot after filtration and the addition of preservative, hereafter called "treated pool." Controls were also performed by testing whole ragweed reaginic sera No. 1 and No. 2 with varying dilutions of ragweed extract. The diluted serum areas were tested with 1:500 ragweed extract since the 1:50 extract was known to produce such marked reactions.

Results.—On the original implantation of the varying dilution series which were carried out in rows (Experiments 3, 4, 5, and 6) there appeared the phenomenon which we had encountered so consistently in all these observations, namely, an "irritation" reaction of redness about the serum dilution series, whealing particularly about the fresh serum pool series, but strikingly enough, no red areola or whealing about the saline series, as a rule.

EXPERIMENT 3 (STUDY D)

INDICATING THE INHIBITING EFFECT OF POOLED SERUM DILUTIONS ON RAGWEED REAGINIC SERUM IS DUE TO SERUM EFFECT RATHER THAN DILUTION ITSELF

Recipient, R. S.

Serum No. 1 undiluted tested with ragweed extract 1:500 ++++
1:5,000
1:50,000

Serum No. 1 diluted with	Saline	Fresh Pool	Treated Pool	S322
1:10	++++	++	0	0
1:100	+++	0	0	0
1:1,000	++	0	0	0
1:10,000	0	0	0	0

Tested with ragweed extract 1:500.

EXPERIMENT 4 (STUDY D)

FURTHER CONFIRMATION OF EXPERIMENT 3

Recipient, E. K.

Serum No. 1 undiluted tested with ragweed extract 1:500 ++++
1:5,000 +++
1:50,000 ++

Serum No. 1 diluted with	Saline	Fresh Pool	Treated Pool	S322
1:10	++++	+++	+	+
1:100	++	+	0	0
1:1,000	0	0	0	0

Tested with ragweed extract 1:500.

EXPERIMENT 5 (STUDY D)

FURTHER CONFIRMATION OF EXPERIMENT 3

Recipient, D. F.

Serum No. 1 undiluted tested with ragweed extract
1:50 ++++
1:500 ++++
1:5,000 ++++
1:50,000 ++++
1:500,000 ++++
1:5,000,000 ++++

Serum No. 1 diluted with	Saline	Fresh Pool	Treated Pool	S322
1:10	++++	++	0	0
1:100	+++	0	0	0
1:1,000	++	0	0	0
1:10,000	0	0	0	0

Tested with ragweed extract 1:500. When tested with 1:50 extract there was a four-plus reaction in the 1:10 dilution made with S322. Reacted four-plus to whole serum originally applied.

EXPERIMENT 6 (STUDY D)

FURTHER CONFIRMATION OF EXPERIMENT 3

Recipient, Mrs. S.

Serum No. 1 undiluted tested with ragweed extract
1:500 ++++
1:5,000 ++++
1:50,000 ++++
1:500,000 +

Serum No. 1 diluted with	Saline	Fresh Pool	Treated Pool	S322
1:10	++++	+++	0	+
1:100	+++	++	0	0
1:1,000	+++	0	+	0
1:10,000	0	0	0	0

Tested with ragweed extract 1:500.

The reactions of the patient's whole serum to varying dilutions of ragweed extract yielded four-plus reactions up to 1:50,000 in most of the tested subjects, and 1:5,000,000 in one (Experiment 5). The results were definitely demonstrated even with the 1:500 ragweed extract which was used in this study because of the marked reactions to 1:50 in the previous study.

Fig. 1.—Photograph showing tendency to maximal reactions with varying dilutions of allergen.

Reactions were displayed in the saline dilutions down to 1:1,000 in some cases, as seen from the tables. The fresh pool dilutions often yielded reactions which were not as intense or in as high dilutions as the saline, but from this point on, there were few or no reactions in the dilution series with treated pool or in the "older" pool taken from stock. It is to be noted that rarely are the scarlet fever pools older than three weeks from the time of bottling, or five weeks from the time of original collection from the convalescent patients. The subject upon whom could be demonstrated passive transfer to ragweed serum No. 1 in a dilution of

1:5,000,000 gave a four-plus reaction to 1:50 ragweed extract when the ragweed serum No. 1 was diluted 1:10 with pooled serum, but none when diluted 1:100. This subject gave no reaction to serum No. 1 diluted 1:10 in the same pool when the testing extract strength was 1:500 (Experiment 5).

Reagins are carried over in dilutions of known reaginic serum when the diluent is saline solution. They are carried over, to some extent, in dilutions made with fresh pooled serum, and least with stock lots of convalescent serum pools. It is not likely that reactions will occur in the ordinary pool when it is noted that a subject who yields reactions to serum No. 1 in a dilution of ragweed extract carried out to 1:5,000,000 yields no reaction to 1:500 extract when the serum is diluted 1:10 in convalescent serum, but does with 1:50 extract. Since the ordinary scarlet fever pool contains from 30 to 50 sera, it does not seem likely that a nonallergic patient treated with convalescent serum containing even a high titer ragweed reaginic serum would encounter a concentration of ragweed pollen sufficient to render him pollen-sensitive even temporarily.

The four-plus reaction of whole serum to varying dilutions of ragweed extract (Fig. 1), used to determine the general sensitivity of the subjects to passive transfer, illustrates and confirms Efron's and Dorfman's[16] findings of the plateau type of reaction curve in which reactions occur practically maximally, if they occur at all—a sort of "all or none" law of reactions. A stronger serum merely produces reactions to higher dilutions, but the quantitative implication does not follow, namely, that theoretical serum "A," which reacts to 10 times the dilution to which theoretical serum "B" reacts, is not necessarily 10 times stronger. It may be more or less than 10 times stronger. It can only be concluded that it is stronger.

STUDY E

Methods.—To catch the intermediate points at which the dilution reactions disappeared, a series of dilutions of sera were carried out with 1:25 and 1:50, as well as the 1:10 and 1:100, mixtures. In addition, a series of similar dilutions in the same subjects was carried out, using only a single, instead of a pooled, serum for dilution purposes. This serum was unfiltered and unpreserved (Experiments 7, 8, 9, and 10).

Results.—In general, the dilutions with a single serum did not inhibit the reaction. This portion of the work was carried out with only one serum, which was from the mother of a ragweed hay fever patient, Mrs. W., who herself gave no reaction to ragweed. The reactions disappeared with the 1:25 and sometimes the 1:50 dilutions, again usually inhibited with stock pools and often carrying through on fresh pools. Two subjects manifested pseudopods when inoculated with 1:25 and 1:50 dilutions of ragweed serum in the single serum.

The single serum dilution in this study does not answer the question of dilution of unpooled sera which was investigated to check the similarity to another type of inhibition phenomenon described below. Inhibition of reactions usually occurs with dilutions below 1:50. Confirmation of the inhibition with treated pools is again offered.

EXPERIMENT 7 (STUDY E)

DETERMINATION OF INTERMEDIATE DILUTION END POINT AND EFFECT OF DILUTION WITH SINGLE AS COMPARED WITH POOLED SERUM

Recipient Mrs. S. reacted with undiluted serum No. 2 to ragweed 1:500,000.

Serum No. 2 diluted with	Saline	Mrs. W.	Fresh Pool	Treated Pool
1:10	+++	+++	+++	+
1:25	+++	+++	0	0
1:50	+	+	0	0
1:100	0	0	0	0

Tested with ragweed extract 1:500. Pseudopods occurred with dilutions in serum of Mrs. W. in 1:10 and 1:25 originally.

EXPERIMENT 8 (STUDY E)

CONFIRMATION OF EXPERIMENT 7

Recipient Mrs. M. reacted to whole serum No. 2 with ragweed extract as low as 1:500,000

Serum No. 2 diluted with	Saline	Mrs. W.	Fresh Pool	Treated Pool
1:10	++++	++++	++++	++
1:25	++++	++++	++++	+
1:50	+++	+++	++++	+
1:100	+	++	+	+
1:1,000	+	+	+	+
1:10,000	+	+	+	+

Tested with ragweed extract 1:50. Pseudopods in dilutions with serum of Mrs. W. in 1:10 and 1:25 originally.

EXPERIMENT 9 (STUDY E)

CONFIRMATION OF EXPERIMENT 7

Recipient C. G. reacted with undiluted serum No. 2 as low as 1:50,000 ragweed extract

Serum No. 2 diluted with	Saline	Mrs. W.	Fresh Pool	Treated Pool
1:10	+++	++++	++++	++++
1:25	+++	+++	++	+++
1:50	+	++	+	+
1:100	+	+	+	+
1:1,000	+	+	+	+
1:10,000	+	+	+	+

Tested with ragweed extract 1:50.

EXPERIMENT 10 (STUDY E)

CONFIRMATION OF EXPERIMENT 7

Recipient M. B. reacted with undiluted serum No. 2 to 1:500,000 ragweed extract

Serum No. 2 diluted with	Saline	Mrs. W.	Fresh Pool	Treated Pool
1:10	+++	+++	++++	+
1:25	+	+	+	+
1:50	+	+	+	+
1:100	+	+	+	+
1:1,000	+	+	+	+
1:10,000	+	+	+	+

Tested with ragweed extract 1:50.

SUMMARY AND DISCUSSION

Reagins expected to be present in convalescent serum are not concentrated enough to be detected by the usual passive transfer technique. These findings must not be translated literally to clinical usage because in the 20 c.c. to 200 c.c. of serum used intravenously, there is 200 to 2,000 times the dose of reagin in 0.1 c.c. used in the passive transfer study. Some sort of reaction does occur, but only in the less than 1 per cent of cases, and true serum-sickness is rarely reported. Most of the reactions are of a blotchy, erythematous nature, often reported as urticarial.

The striking inhibition or "blocking" of the transfer reaction when serum of known high reaginic titer is diluted with convalescent pooled serum indicates that some neutralization, possibly of a colloidal nature, occurs under these circumstances. The clinical support of this observation is the impunity with which pooled serum is administered intravenously. Further support of this phenomenon is offered along similar lines in the case of inhibition of hemagglutinins which Levinson and Kronheim[17] have demonstrated, and which they related to us upon the announcement of our findings. These workers tried to discover some objective evidence to warrant the safe use of mixed serum in varying quantities intravenously without regard to the blood type of the patient. In the course of their studies they found that serum, even a single serum, inhibits the action of hemagglutinins. For instance, they found that a type A serum which agglutinates type B cells in a dilution of 1:64 in a saline solution agglutinates only as far as 1:3 when the serum is diluted with serum, pooled or single. They felt, therefore, that the recipient's own serum would inhibit any agglutinating effect of pooled convalescent serum used therapeutically, and again clinical results have borne out this thesis.

The inhibitory effect toward reagins in convalescent serum is most marked in pooled sera which have been prepared for some time. It is less effective in pools freshly filtered and treated with preservative and least effective in fresh pools before these measures are taken. Saline dilutions of serum and dilutions prepared in a single fresh serum have little or no inhibiting effect. The "blocking" effect is a property of serum, and this seems to be influenced by the treatment and age of the serum.

In the course of the observations, occasionally a subject reacted more strongly with an allergen on her own skin site than upon one treated with convalescent serum. This may be interpreted as a local inhibitory effect of the serum on the recipient's native reagins. This seems to indicate that pooled serum possesses general desensitizing properties.

Numerous instances of the immediate irritating and even allergically reacting effects of pooled, fresh, and even autogenous sera have been encountered without any apparent influence on the subsequent reactions with allergens.

The rationale prompting the search for reagins in convalescent serum was based on the law of probabilities that a pool of any appreciable number of bloods commonly employed in the collections of this therapeutic agent must contain serum of higher or lower concentration from allergic persons. It was concluded that tests for reagins on enough subjects to allow the reagins to manifest themselves against strong concentrations of allergenic extracts would yield the answer. In the first study it might be inferred that the mothers of allergic children were a hand-picked lot whose findings might not be valid, but even in this group, the findings were practically negative. Ironically enough, when a non-selected group of mothers was next engaged, 10 of the 30, or 33 per cent, were themselves allergic, and half of the entire group came from families with allergy.

Finally, the inhibiting effect of pooled convalescent serum on its presumably contained reagins, as well as on reagins artificially introduced, may be expected to be exerted against other or all reagins. It would seem to follow logically that such serum should have a definite therapeutic value by cancelling one of the factors necessary in the production of allergic symptoms, namely, reagin. Work to investigate this possibility is in progress.

CONCLUSIONS

1. Convalescent serum does not yield evidence of reagins which might be anticipated from the probability that pools include blood serum from allergic persons.

2. Pooled serum to which known high reaginic ragweed serum has been added likewise fails to disclose ragweed reagins by passive transfer.

3. Further studies indicate that the inhibiting effect is due to the serum rather than the factor of dilution itself.

4. The inhibiting effect is strongest in stock pools, less strong in fresh pools, and least strong in single serum and fresh pools before Berkefeld filtration and treatment with preservatives.

5. The possible therapeutic effect of pooled sera, fluid or lyophilized, is suggested and is being investigated.

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DISCUSSION

DR. GEORGE L. WALDBOTT, Detroit.—I have little to contribute to the experimental side of this work but should like to add a few words concerning its practical application. Since 1932, fifty-eight transfusions have been done in my office with both normal serum and serum from convalescing asthmatics to patients with more or less severe asthma. On three occasions urticaria followed the transfusion within about half an hour. It was, however, readily controlled by epinephrine.

One of my patients not included in this series had a rather severe shock following a transfusion give by her physician in another town. The doctor had not employed the precautions which we usually use, namely, giving a preliminary skin test with the donor's blood and then administering a small amount of blood intravenously in order to recognize any possible ill effect. He also administered novocain from which the patient had previously suffered a strong generalized reaction during a tooth extraction. If the preliminary skin test is positive, it is advisable to discard the blood. As Dr. Tumpeer mentioned, the patient should not eat any food for several hours before the transfusion, as such food may account for reactions if the recipient of the blood is sensitive to it.

SUBCUTANEOUS TISSUE PRESSURE STUDIES IN URTICARIA AND ANGIONEUROTIC EDEMA*

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IT IS generally assumed that the site of the allergic reaction is in the living cell. Chemical theories postulate reaction changes within the cells, while the physical theories localize the reaction on the cell surface. There is as yet no conclusive proof whether all types of body cells may participate in the reaction or whether it is limited to certain groups. Vascular endothelial cells, particularly those of the reticuloendothelial system, smooth muscle cells, and hepatic cells are rather generally considered to play a special role in the allergic response.

If the reaction site is in or on the living cell, we may anticipate that, as appropriate methods become available, these will be applied more directly to study of the activities of the cell itself. The outstanding example already applied is that of study of contraction of uterine horn muscle according to the Schultz-Dale technique.

While much has been learned concerning the allergic response in study of changes in the blood and its circulation, it is obvious that we are here studying secondary changes or end results of the reaction. The extravascular, extracellular fluid or interstitial tissue fluid is located one step nearer to the cell itself (with the exception of the vascular endothelium), and it has seemed to the authors that its study might eventually add something to our knowledge of the altered physiology of allergy. There is as yet no large number of methods available for such study, but the perfection by Burch and Sodeman of a technique for the clinical study of subcutaneous tissue pressure or tissue tension has made it possible to study this manifestation of functional changes in the subcutaneous tissues, or elsewhere, as in the muscles.

TISSUE FLUID

Seventy per cent of the body weight is represented by water. Of this, 50 per cent is intracellular, while approximately 5 per cent is contained in the blood plasma. Fifteen per cent of the body weight is represented by interstitial, extracellular fluid. Of the extracellular fluid of the body, only one-fourth is found in the blood channels, while three-fourths is situated within the tissues.

Gamble has emphasized that one function of tissue fluid is to maintain the stability of the volume of fluid in the vessels. He speaks of the extracellular fluid as a single fluid lying in two compartments (inside

*Presidential address read before the Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., April 29, 1939.

and outside the vessels) and "equipped with a device (plasma protein) for producing movement from the interstitial space into the vascular compartment." The importance of the fluid reserve is seen especially in the phenomenon of dehydration. Loss of fluid occurs usually as a result of failure of absorption or reabsorption of fluid, most generally as the result of persistent vomiting or diarrhea. Gamble observed in experimental dehydration that, although loss in body weight was recorded from the first day, the animal remained apparently well and plasma protein remained at normal levels until the tenth day. During the next four days, until death, weight loss increased more rapidly, and the plasma protein concentration increased very rapidly. This explains why, except in the terminal stages, plasma protein determination constitutes an unreliable indicator of dehydration, while body weight determinations are much more helpful. Until the reservoir is quite thoroughly depleted, that portion of extracellular fluid which is in the vascular system remains relatively unimpaired.

Gamble also emphasized the importance of electrolytes, especially sodium, in the maintenance of normal tissue fluid reserve. However, this is not a part of the present discussion.

Present understanding of the anatomy of the lymphatics is that these channels are dead-end, with a complete lining of endothelium, and not directly continuous with the interstitial spaces. We may therefore look upon the interstitial fluid as lying in a closed space between the endothelium of the capillaries and that of the lymphatics, a space which also contains cells, connective tissue fibrils, etc. If we follow the fluid in its progress from the arterioles into the capillaries at the arterial end of the capillary beds, out into the tissue spaces, and back through the capillaries at the venous end, or into the lymphatic capillaries, we may observe that three factors combine to retain water within the vascular channels: the colloid osmotic tension of the plasma protein; relative capillary impermeability; and tissue tension, which is the pressure of fluid in the tissue spaces outside of the capillaries. Factors which promote the passage of fluid into the tissue spaces are: the hydrostatic pressure of the blood; the osmotic tension within the tissue spaces; and the relative capillary permeability.

Wiggers has illustrated in a simple manner the filtration-absorption mechanism between the capillaries and the tissue spaces. Assuming an osmotic pressure within the blood vessels of 35 mm. and a hydrostatic pressure in the proximal capillaries of 45, the direction of fluid flow will be outward, into the tissue spaces. In the distal capillaries the hydrostatic pressure has been reduced to about 16 mm., while the osmotic tension remains the same (35). The direction of flow will, therefore, be reversed at this point, passing from the tissues back into the vessels. In this way there develops an actual circulation of fluid in the tissue

spaces. Other factors such as capillary permeability, tissue tension, and tissue osmotic pressure will influence this circulation in one way or another, depending upon the condition of the moment. A combination of all of these factors will determine the actual tension of the fluid in the tissue spaces.

The precise method by which water is transported through the spaces is still a matter of conjecture. McMaster and Parsons have made a recent contribution to this study. They state, "That an extravascular movement of water and other substances exists, no one doubts, but how this transport takes place, no one knows. Do actual spaces exist between the formed elements of the tissues? If so, is there a circulation of tissue fluid through them?" These authors concluded, from microscopic study of the passage of dyes outward through the walls of lymphatic capillaries, that such substances, of large molecular weight, pass through the tissue spaces on the surface of or between the connective tissue fibrils. They found that, normally, transport occurs along these fibrils and they interpreted this as evidence of the existence of a tissue matrix. Under normal conditions they found no free interstitial fluid although, with the development of irritative edema, the dye passed out from the fibrils into free spaces, presumably containing free edema fluid.

Cowdry, who discussed changes in the tissue fluids during the process of aging, described fibrils which were apparently "formed directly from tissue fluids by some process of concentration and alignment of tissue fluid components, or by cells under the influence of tissue fluids. The case for fibrils of the collagenic variety is a little clearer than for the rest." He inclined to the acceptance of the concept of a gel-like intercellular material in the tissue fluids, which varies with the physiologic age and development of the connective tissue and which varies in different types of tissues.

A prevailing concept today may be said to be, therefore, that tissue fluids contain a gel-like matrix with fibrils along which particles of large molecular weight appear to be transported, and that in the presence of edema, free fluid may also exist in multiple minute areas of the tissue spaces. We must await further studies for a clearer understanding of the normal fluid circulation in the spaces.

TISSUE TENSION

Tissue pressure has been defined as the pressure with which the tissue structures resist any change in their anatomic relationship—the pressure which resists deformation or distention. We may also describe it in the phraseology of Landerer who, in 1884, first undertook study of tissue tension as "the pressure required to force fluid into tissues." This is especially appropriate since it is what one actually does in the clinical determination of tissue pressure. We assume that the threshold of this pressure from without is equal to the opposed pressure existing within.

The apparatus adapted by Burch and Sodeman as a modification of the earlier Riml-Henderson technique is quite simple. The opening in the beveled end of a 26 gauge needle is occluded with solder, and four openings are drilled symmetrically into the distal third of the needle's wall, using a jeweler's drill. This needle is connected with a glass adapter of 1 mm. bore, etched at 1 mm. intervals to facilitate reading of slight movements of a meniscus. This is next connected with a T-tube or Y-tube, to one arm of which a rubber bulb is attached, while the other arm is connected with a U-tube water manometer. The rubber pressure bulb is controlled with a small screw clamp.

Sterile physiologic saline solution is drawn into the needle and to about halfway along the glass adapter which serves as a window. The pressure in the system is brought to equal the atmospheric pressure. The needle is inserted into the subcutaneous tissue. If the tissue pressure is high, the meniscus in the window will be seen to start an outward movement. The pressure in the system is increased by means of the screw clamp until the meniscus returns to its original position and the system stands in equilibrium. The pressure in millimeters of water is read from the manometer. If the meniscus does not move, pressure is slowly increased until the former just commences to move toward the needle. This pressure is taken as the tissue pressure. Readings are made in triplicate under aseptic conditions. In routine studies, the pressure is determined at a site so arranged as to be at heart level, usually with the patient supine.

In serial determinations over periods of time the needle must be removed and reinserted since, when it remains in situ, the readings gradually decrease. Since Burch and Sodeman observed different tensions in different portions of the body, such as the hand, forearm, and foot, even when at heart level, it is important when determining the pressure in a given pathologic area, such as an urticarial wheal, to make a control determination at a symmetrical uninvolved site. They found mean ranges in various localities from 17.9 to 30.8 mm. Maximal normal variations were from 8 to 54 mm. Persons with congestive failure and increasing edema showed higher pressures, ranging from 47 to 262 mm., when determined in the pretibial area. In receding cardiac edema, values were lowered, sometimes even to below normal. Hypertension appeared to have no direct influence upon the tissue pressure.

In a later report, Sodeman and Burch reported the normal value for subcutaneous tissue pressures in the volar surface of the forearm and pretibial area, at heart level, as ranging from 11 to 54 mm. They found varying increases in congestive heart failure, beriberi, nephritic edema, nephrotic edema, scleroderma, pernicious anemia, toxemia of pregnancy, and erysipelas. In one experiment the subcutaneous injection of histamine produced a local increase to 246 mm.

EXPERIMENTAL DATA

Any attempt to apply this method to the study of allergy necessitates a preliminary determination of the customary tissue response in a local allergic reaction, such as an urticarial wheal or angioneurotic edema. The present paper comprises such a study. Other possible applications will be discussed.

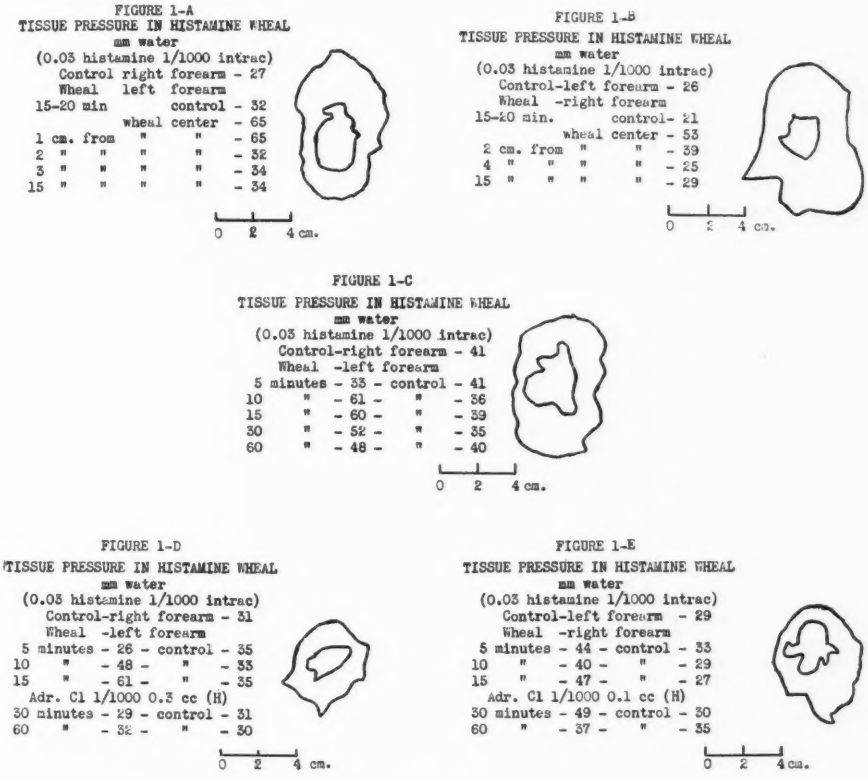
FIGURE 1-A
TISSUE PRESSURE IN HISTAMINE WHEAL
mm water
(0.03 histamine 1/1000 intrac)
Control right forearm - 27
Wheal left forearm
15-20 min control - 32
wheal center - 65
1 cm. from " " - 65
2 " " " " - 32
3 " " " " - 34
15 " " " " - 34
0 2 4 cm.
FIGURE 1-B
TISSUE PRESSURE IN HISTAMINE WHEAL
mm water
(0.03 histamine 1/1000 intrac)
Control-left forearm - 26
Wheal -right forearm
15-20 min. control- 21
wheal center - 53
2 cm. from " " - 39
4 " " " " - 25
15 " " " " - 29
0 2 4 cm.
FIGURE 1-C
TISSUE PRESSURE IN HISTAMINE WHEAL
mm water
(0.03 histamine 1/1000 intrac)
Control-right forearm - 41
Wheal -left forearm
5 minutes - 33 - control - 41
10 " - 61 - " - 36
15 " - 60 - " - 39
30 " - 52 - " - 35
60 " - 48 - " - 40
0 2 4 cm.
FIGURE 1-D
TISSUE PRESSURE IN HISTAMINE WHEAL
mm water
(0.03 histamine 1/1000 intrac)
Control-right forearm - 31
Wheal -left forearm
5 minutes - 26 - control - 35
10 " - 48 - " - 33
15 " - 61 - " - 35
Adr. Cl 1/1000 0.3 cc (H)
30 minutes - 29 - control - 31
60 " - 32 - " - 30
0 2 4 cm.
FIGURE 1-E
TISSUE PRESSURE IN HISTAMINE WHEAL
mm water
(0.03 histamine 1/1000 intrac)
Control-left forearm - 29
Wheal -right forearm
5 minutes - 44 - control - 33
10 " - 40 - " - 29
15 " - 47 - " - 27
Adr. Cl 1/1000 0.1 cc (H)
30 minutes - 49 - control - 30
60 " - 37 - " - 35
0 2 4 cm.

Fig. 1.

Tissue Pressure in Induced Histamine Wheals.—In each case, 0.03 c.c. of histamine 1:1,000 was introduced intracutaneously. Tissue pressure was determined in triplicate in the subcutaneous tissues immediately under and at varying distances from the center of the wheal. Symmetrical controls were used when indicated. Determinations were made at heart level. It will be seen from Fig. 1*A* that the increased tension scarcely extended beyond the margin of the wheals, the reading 2 cm. from the center being the same as the control, even though still within the region of flare. In Fig. 1*B* there was some increased tension outside of the wheal (2 cm.) but not beyond the margin of the flare (4 cm.). There was no increase in tension in the control areas following local histamine injections. This indicates that change in subcutaneous tissue

tension is purely local in the response to the dose of histamine given endermally and is not reflected in any systemic change or even in changes immediately outside the area of visible reaction. Determinations were made fifteen to twenty minutes after histamine injection.

The rapidity with which the reaction develops is illustrated in Fig. 1*C*. Five minutes after injection there was no notable local increase in the pressure determined approximately at the site of piqûre. After ten minutes, and before the wheal had reached its full evolution, the tension had reached a maximum. This was not increased further at the end of fifteen minutes when the wheal was well developed. There was evidence of gradual subsidence at sixty minutes. We may interpret this as being what one would anticipate during the process of reaction—that tension is high during increasing edema. This corresponds with the observations of Burch and Sodeman in the edema of congestive heart failure. It is a phenomenon which would be necessary in the production of swelling. Fig. 1*D* shows a slightly slower evolution of increased pressure, while Fig. 1*E* indicates that the sequence is not altogether consistent, the highest reading being obtained after thirty minutes and after an injection of adrenalin. However, the difference in Fig. 1*E* is slight and within the range of technical error.

The effect of the hypodermic injection of a therapeutic dose of adrenalin chloride 1:1,000 in the control arm, remote from the site of study, is illustrated in Figs. 1*D* and 1*E*. In one instance, the pressure had returned to normal within thirty minutes, while in the second, it had not returned to normal at that time, but was normal at the end of sixty minutes.

We may say that these histamine observations are what one would anticipate in view of the present understanding of the physiology of whealing. The actual measurement of the changes in tension, which has not been previously recorded, has some value for reference purposes.

Induced Allergic Wheals.—Tissue tension determinations were made on a total of 40 wheals in positive skin reactions obtained in the course of diagnostic allergic studies. These represented reactions to foods, pollens, and other inhalants, such as dust, feathers, and orris root. Reactions were studied on the back, arm, and forearm. Symmetrical control determinations were made. Seventeen of the positive reactions were to scratch testing, while the remainder were endermal. Positive scratch reactions showed as much increase in tension as did positive endermals, the maximum reading for each being 102 mm.

With one exception (Table I, Subject 2), normal control readings fell within the normal range established by Burch and Sodeman.

McConnell described a variation in the intensity of allergic and histamine wheals in different parts of the integument, the skin of the back and abdomen reacting more intensely than that of the extremities.

TABLE I

TISSUE PRESSURE IN INDUCED CUTANEOUS WHEALS IN MILLIMETERS OF WATER

SUBJECT	SITE	METHOD	CONTROLS		MAX. WHEAL READING	MIN. WHEAL READING	MEAN WHEAL READING	NO. OF WHEALS
			SITE	READING				
			1*	42				
1	Back	Endermal	2†	44	64	38	49	8
			1	31				
2	Back	Endermal	2	59	74	50	62	2
			1	18				
3	Back	Endermal	2	23	80	42	59	3
			1	40				
4	Back	Endermal	2	29	102	102	102	1
			1	50				
5	Back	Endermal	2	38	60	52	56	2
	Volar surface of forearm	Scratch	1	50				
			2	38	69	69	69	1
			2	14				
6	Arm	Endermal	3††	21	61	36	48.5	2
7	Volar surface of forearm	Scratch	2	23				
			3	18	102	45	59	16
			1	23				
8	Back	Endermal	2	17	40	17	27.6	5
Total number of wheals								40
Mean wheal reading							59.1	
Minimum wheal reading						50.1		
Maximum wheal reading					72.4			
Mean control reading				32.1				

*Control 1, suprascapular area.
†Control 2, volar surface of forearm.
††Control 3, inner aspect of arm.

Vaughan has reported similar conclusions. In the present small series of eight cases there was no clearly defined difference in normal tissue tension in different areas, the control readings on the back ranging from 18 to 50 mm.; on the arm, from 18 to 21 mm.; and on the forearm, from 14 to 59 mm. Similarly there was no clearly marked variation in tissue tension beneath positive wheals in these different areas.

This is what one would anticipate, in view of the fact that the wheals in all localities varied in intensity of reaction. In Table II, it will be seen that, irrespective of the site of testing, the more intense the reaction, the greater was the resultant tissue tension. This applied equally to scratch and endermal reactions.

Angioneurotic Edema.—Two patients with chronic circumscribed edema of the angioneurotic edema type and one with recurrent acute circumscribed edema comprised the subject material for this study. Subject I, Fig. 2, is representative of the first two. She has a chronic edema of the lower lip which has been present for several years. Ingestion of foods to which she is sensitized produces an acute exacerbation with a great increase in local swelling, which may last for several hours. Emotional disturbances, anger, and anxiety will do likewise, and to a

TABLE II

TISSUE PRESSURE READINGS IN MILLIMETERS OF WATER IN CUTANEOUS WHEALS OF VARIOUS DEGREES

SUBJECT	1-PLUS				2-PLUS				3-PLUS				4-PLUS				5-PLUS				7-PLUS			
	MINIMUM	MAXIMUM	MEAN	NUMBER	MINIMUM	MAXIMUM	MEAN	NUMBER	MINIMUM	MAXIMUM	MEAN	NUMBER	MINIMUM	MAXIMUM	MEAN	NUMBER	MINIMUM	MAXIMUM	MEAN	NUMBER	MINIMUM	MAXIMUM	MEAN	NUMBER
1	38	51	45.5	3	49	64	58	3																
2					50	50	50	1	74	74	74	1												
3					55	42	49.4	2					80	80	80	1								
4																					102	102	102	1
5					52	52	52	1	60	69	63.8	2												
6									36	36	36	1	61	61	61	1								
7					45	58	51	3	45	73	60.6	5	62	91	82	5	84	102	98	3				
8					17	40	27.6	5																
Avg.	38	51	45.5		44.6	51	48		53.7	63	58.6		67.6	77.3	74.3		84	102	98		102	102	102	

like degree. By following allergic dietary restrictions and avoiding emotional disturbances, she has decidedly lessened the swelling, but some edema persists. In such intervals the tissue pressure remains elevated (from 128 to 180 mm.) (Fig. 3). Tissue tension in the forearm is normal (21 to 31 mm.).

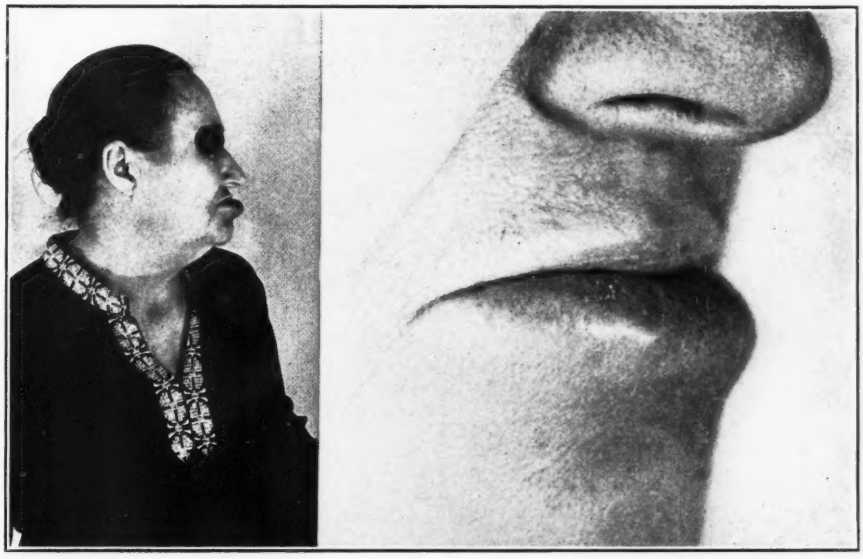

Fig. 2.

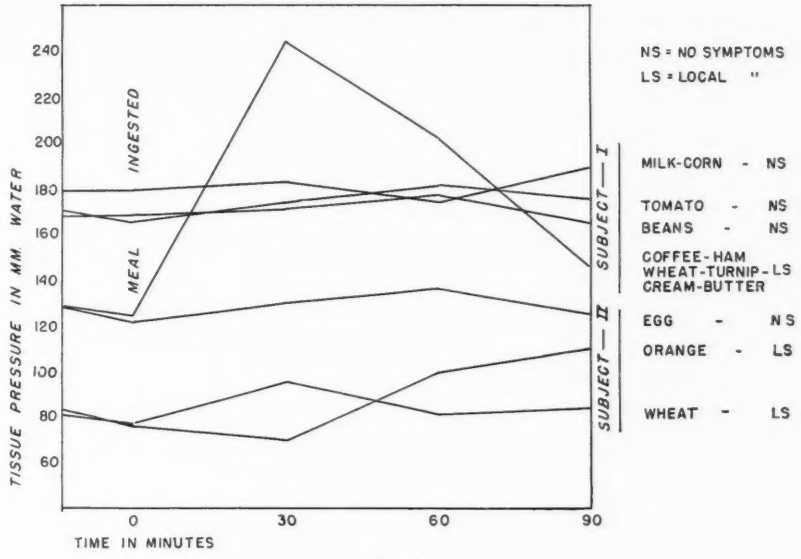

Fig. 3.

After the ingestion of a meal containing foods to which she is allergic (coffee, ham, wheat, turnip), there was decided increase in the local

symptoms, and the tension rose from 128 to 242 mm. Control tests with nonallergenic foods (milk, corn, tomato, and bean) caused no increase of the pre-existing level.

In Subject II, eggs, which were not allergenic, produced no increase in tension. Orange, to which the patient was allergic, caused an increasing edema of the left cheek, and the tension rose about 25 mm. Wheat, which was also allergenic and caused local swelling, produced only very slight temporary increase.

We may conclude that local reactions to known allergenic excitants carried to the areas in the blood stream after enteral absorption will produce varying degrees of increase of tissue tension, without detectable change in the general tension as determined elsewhere in the body in control sites.

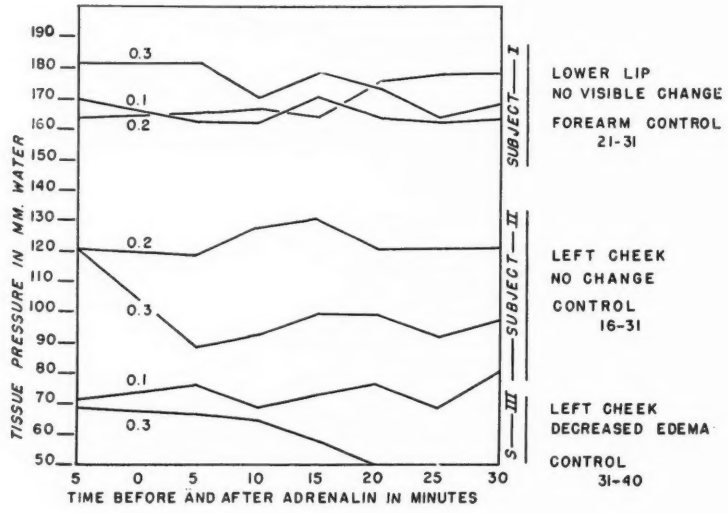

Fig. 4.

The effect of the injection of adrenalin at a remote site, as in routine clinical use, was studied. It was found (Fig. 4) that the customary therapeutic dose, 0.3 c.c. of a 1:1,000 solution, produced decrease in local tissue tension, while subtherapeutic doses of 0.1 c.c. and 0.2 c.c. were ineffective.

DISCUSSION

While the preceding observations are of interest solely as records of physiologic alterations, some interesting questions arise.

Would determination of tissue tension have any diagnostic value? Could one tell, thereby, whether or not a subject is in the allergic group? With the information available, this is highly improbable. Tissue tension appears to be within the normal range among allergics except where local reaction occurs, and even here the alterations appear only to

parallel the visible physical changes. Persons with urticaria were found to have normal tension in normal areas of skin. Two patients with severe asthma at the time of testing, but without skin lesions, showed normal skin tensions. The three patients with circumscribed edema showed normal findings in normal areas of skin even though they were reacting acutely in the local area to ingestion of allergenic foods.

It is possible that the procedure might have some value in assaying the therapeutic effectiveness of drugs by comparison with the response to epinephrine as illustrated in Fig. 4.

The method presents a possible approach to further study of the physiology of clinical and experimental anaphylactic shock. The suggestion has been made by Waldbott and others that, in the constitutional reaction, we are dealing with a more or less universal increase in capillary permeability with consequent generalized tissue edema. This would explain the rapidity of development of shock, with its very low blood pressure, the increased blood concentration as observed by Black and Kemp, and the inconstant increase in blood osmotic pressure observed by Mayer and Fleisher. Three of the chief factors which control the movement of fluid into the tissue spaces are capillary hyperpermeability, colloidal osmotic tension within the tissue spaces, and tissue turgor or resistance to further distention. These are of more importance than hydrostatic pressure since Cowdry reports no evidence of alteration in equilibrium of the tissue fluid in vascular hypertension. Krogh has concluded that the total area of the capillaries of the muscles alone is approximately 6,300 square meters, or more than 3,000 times the entire body surface. It has been estimated that, in the absence of restraining forces such as those mentioned, the entire plasma volume could pass from the capillaries into the tissues within ten seconds.

The question arises, therefore, whether in acute anaphylactic shock one would be able to demonstrate generalized increase in subcutaneous tissue tension, in contrast to its absence in the conditions herein studied. Opportunity for study of anaphylactic shock in human subjects is fortunately rare, and when it does occur, it is likely to be overlooked in the emergency. Fortunately the phenomenon may be produced experimentally. The writer sensitized twelve guinea pigs to horse serum. Unfortunately, in the heat of the summer all but two died of natural causes. One month after the sensitizing injection, these two were shocked by the intracardial injection of normal horse serum.

Prior to the shocking dose, tissue tension was determined subcutaneously in the skin of the abdomen. In Pig 1 these control determinations were found to be 22.2 and 24.7 mm. of water. Two cubic centimeters of horse serum was then given intracardially. One minute later the tissue tension was 19 mm.; two minutes later it was 30. Five minutes later and nine minutes later it was 20 mm. The pig recovered.

Control readings in Pig 2 were 26.9 and 27.3 mm. Three cubic centimeters of horse serum was given intracardially. One minute later the subcutaneous abdominal tension was 46 mm. Two minutes after injection the animal was apparently dead, and the tension was 34 mm. After three minutes the animal was definitely dead, and the tension was 35. At nine minutes, it was 20; at twelve, it was 15; at eighteen, it was 11; and at twenty, 17.

In the pig which succumbed there was increased tension at a site remote from injection, well on toward double the control reading. The part that convulsive movements might have played in this was undetermined.

These findings are merely suggestive but indicate the desirability of continued investigation in this direction.

SUMMARY

A new method of approach to the study of the physiology of whealing and of tissue edema, especially as it applies to the allergic reaction, is presented. This consists in the application of the clinical method for determining subcutaneous tissue pressure, devised by Burch and Sodeman. The possibilities of its use in allergic investigation are discussed.

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201 WEST FRANKLIN STREET

SUMMER HAY FEVER OF UNKNOWN ORIGIN IN THE SOUTHEAST

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IN NOVEMBER, 1935, in a paper entitled "Hay Fever in Alabama,"* I analyzed 100 cases of hay fever and called attention to the fact that 22 per cent of these occurred in the summer and that in over half we had been unable to demonstrate sensitization to pollens. In every respect, the symptoms of these patients with negative skin tests were typical of seasonal hay fever due to pollen sensitivity. The onset was generally sudden, the symptoms becoming rapidly more severe. The symptoms were present almost daily throughout the long period of the summer months and ended gradually with the approach of cold weather. There were daily variations in intensity, and most of the patients were the worst in the morning, complaining also of an increase in intensity between 9:00 and 11:00 P.M. The appearance of the nasal mucous membrane was typically pale and boggy, and smears of the nasal secretion showed a preponderance of eosinophile cells. There was also a blood eosinophilia of variable extent. Asthma was a frequent complication.

Since that time I have studied forty-seven cases which we consider so typical that we feel justified in considering them as a clinical entity. Because the cause of these summer cases remains undetermined, we have referred to them as cases of "summer hay fever of unknown origin." This paper is a summary of our knowledge of this type of hay fever.

DEFINITION

In order that there may be no misunderstanding as to the type of case included in this series, we wish to emphasize that we excluded patients who, although they did not react to pollens, gave positive skin tests to some emanation or inhalant with which they had seasonal contacts. We excluded also those patients who had hay fever for a period of one or two months during the summer, including only those whose symptoms began around May and ended in September or October and who gave no positive reactions to any of the pollens, inhalants, or molds on skin or ophthalmic testing. Two-thirds of our patients stated that their symptoms began in May, the others dating their symptoms from the latter part of April or the early part of June. All of these

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patients had symptoms continuously through September and about three-fourths of them throughout the early part of October.

GEOGRAPHICAL DISTRIBUTION

From our own experience, we can say that this type of hay fever occurs in the southeastern quarter of the state of Alabama and in northwest Florida exclusive of the coastal region. Several of our patients were free of symptoms in Panama City, Fla., and a few stated that they were relieved in Miami, Chicago, South Carolina, North Carolina, and New York City. From the combined experience of Efron* and Wodehouse,† who have made surveys of the experiences of twelve and thirty-four allergists, respectively, the following information is taken. Only a few of the total number questioned reported encountering this type of hay fever. Waring found cases of unknown origin in Charleston, S. C., but he did not report the percentage. The season there lasted from "late spring to early fall." Wright of Atlanta, Ga., reported that from 10 to 15 per cent of his seasonal hay fever cases were "summer hay fever of unknown origin." The season there lasts from the end of May until fall. In Savannah, according to Metts, the season extends from May 1 to October 1 with 30 per cent of the cases in this group. In Macon, Ga., Porch reported that the season extends from May 10 to frost with 5 per cent in this group. Heinberg of Pensacola, Fla., stated that 20 per cent of the summer cases belong to this group and that the season extends from June to October. Efron in New Orleans reported 65 per cent of summer hay fever cases as belonging to this group, the season there extending from April until October. Another observer in New Orleans reported only 20 per cent. One observer in Houston, Texas, reported the season as extending from May 15 through September 30, with 10 per cent of the summer cases in this group. Hosen reported that in Port Arthur, Texas, the season extends from May 30 to September 30 with 50 per cent of the hay fever cases in this group.

In the following cities, allergists reported no summer hay fever of unknown origin: Birmingham and Mobile, Ala.; Memphis, Tenn.; Greenwood, Jackson, and Natchez, Miss.; Gainesville, Jacksonville, West Palm Beach, and Miami, Fla.; McRae, Ga.; and Dallas, San Antonio, Abilene, Waco, Corsicana, and Fort Worth, Texas. From Memphis, Birmingham, Houston, and Atlanta have come reports of cases of unknown origin, but the season extends from May 15 to July 1 or from April 15 to July 15. These cases may belong to the group under discussion, the season being of shorter duration at the margins of the affected areas. Further reports from these cities would be of value.

*Personal communication.
†Unpublished study in collaboration with the author.

From the above information, Wodehouse has prepared a map outlining the probable range of summer hay fever of unknown origin (Fig. 1). Roughly speaking, it covers the southern coastal plain, except peninsular Florida and all of the beaches from which reports have been received. Savannah and Brunswick Beaches in Georgia, Jacksonville Beach and Panama City in Florida, Biloxi in Mississippi, and Galveston in Texas are reported to be free of this type of hay fever. Changes may be necessary in outlining the affected area when reports have been received from other allergists working near the boundary line.

Fig. 1.—Map showing area from which summer hay fever of unknown origin has been reported. The dotted line indicates the boundary of the area.

STUDIES IN ETIOLOGY

Trees.—Most of the trees in Alabama have completed their period of pollination by May 15, the chief exceptions being black walnut *(Juglans nigra)* and ironwood *(Carpinus caroliniana)* which continue until June 15. Birch *(Betula alba)* and beech *(Fagus grandifolia)* pollinate through the entire month of May; the Chinese elm *(Ulmus serotina)* pollinates in the fall. We have tested many of our patients with a large group of tree pollens and practically all of them with pecan *(Hicoria pecan)*, oak *(Quercus spp.)*, and elm *(Ulmus americana)*, and

the results have been negative. We are certain that tree pollens play no part in the production of summer hay fever of unknown origin.

Grasses.—On first thought one might assume that grass pollen is responsible for all summer hay fever. Certainly, the grasses are the only plants which pollinate throughout all the months from May to October. Bermuda grass *(Capriola dactylon)* and Johnson grass *(Holcus spp.)* pollinate throughout the entire period, and there are many other grasses

TABLE I

RESULTS OF TESTS WITH GRASS POLLENS

GRASS POLLEN	CUTANEOUS	INTRADERMAL	OPHTHALMIC	POSITIVE REACTIONS
Rye grass, *Lolium perenne*	39	10	7	1 doubtful ophthalmic
Bermuda, *Cynodon dactylon*	44	40	16	1 doubtful ophthalmic
Timothy, *Phleum pratense*	46	33	6	
Annual blue grass, *Poa annua*	42	12	6	
June grass, *Poa pratensis*	29	10	4	
Orchard grass, *Dactylis glomerata*	28	28		
Meadow fescue, *Festuca elatior*	40	0	1	
Crab grass, *Syntherisma sanguinale*	40	2	0	
Brome grass, *Bromus inermis*	41	0	0	
Paspalum, *Paspalum spp.*	43	1	4	
Panic grass, *Panicum spp.*	36	1	1	
Barnyard grass, *Echinochloa crus-galli*	26	0	3	
Corn, *Zea mays*	42	25	2	1 doubtful cutaneous; 1 doubtful intradermal
Sudan grass, *Sorghum vulgare sudanense*	32	7	0	
Crab grass, *Digitaria sanguinalis*	40	11	3	
Redtop, *Agrostis alba*	38	16	1	
Foxtail, *Setaria spp.*	6	0	0	
Sweet vernal, *Anthoxanthum odoratum*	27	0	2	
Millet, *Panicum miliaceum*	10	13	0	1 doubtful intradermal
Quack grass, *Agropyron repens*	19	0	0	
Canary grass, *Phalaris canariensis*	17	0	0	
Wild oats, *Avena fatua*	19	0	0	
Velvet grass, *Holcus lanatus*	3	0	0	
Darnel, *Lolium temulentum*	4	0	0	
Johnson grass, *Sorghum halapense*	49	52	22	3 doubtful cutaneous; 8 doubtful intradermal; 7 doubtful ophthalmic
Goose grass, *Eleusine indica*	19	0	0	
Bent grass, *Agrostis alba*	5	0	0	

which bloom for a shorter period during the summer months. Our patients have been tested with a large number of grasses and with the more important pollens, not only by scratch test with dry pollens and by intradermal tests with 4 per cent solutions, but many of them also by the ophthalmic and nasal methods. In some cases, patients were treated with large doses of grass pollen extracts with no relief.

In Table I we have listed the grasses tested, the number of cutaneous, intradermal, and ophthalmic tests made with each pollen, and the number of positive reactions obtained. From this experience I am convinced that either grass pollen plays no part in the production of symptoms in this type of hay fever or that some grass has been overlooked which, though comparatively local in distribution, produces large amounts of pollen. Wodehouse, who spent some time in Alabama studying the flora, is convinced that grasses have been definitely ruled out by this investigation and that, if the cause of summer hay fever of unknown origin is some grass not yet investigated, at least some of the patients should react to one or more of the grass pollens tested. With 27 different grass pollens, representative of the chief families of *Gramineae*, I have made 884 cutaneous tests with 4 doubtful reactions, 261 intradermal tests with 10 doubtful reactions, and 78 ophthalmic tests with 9 doubtful reactions. In no case was a definitely positive reaction obtained.

Weeds and Flowering Plants.—Table II summarizes my experience with summer weeds and flowering plants. With 35 weed and flowering plant pollens, 975 cutaneous tests, 231 intradermal tests, and 13 ophthalmic tests were made. There were 2 doubtful cutaneous, 2 doubtful intradermal, and 1 doubtful ophthalmic reactions only. I am convinced that this group of plants is not responsible for summer hay fever of unknown origin.

There has been sufficient evidence in the past to prove that the flowering plants play no part in the production of hay fever, except in those individuals, like gardeners or florists, who come in direct contact with the flowers. Patients, on the other hand, are always convinced that their symptoms are due to some conspicuous flower, and it seemed wise to test with pollen of some of the more common varieties. Rauth has suggested that althea might play a part, but I have had no personal experience with it. Porch has suggested that the privet might be the etiologic factor, and Efron suspected the same plant. Privet *(Ligustrum vulgare)* pollen has been tested cutaneously 34 times, intradermally 23 times, and by ophthalmic test 4 times, with one positive intradermal and one positive ophthalmic reaction. It seems obvious that weeds and flowering plants are not responsible for summer hay fever of unknown origin.

TABLE II

RESULTS OF TESTS WITH POLLENS OF SUMMER WEEDS AND FLOWERING PLANTS

POLLENS	CUTANEOUS	INTRA-DERMAL	OPHTHALMIC	POSITIVE REACTIONS
Sheep sorrel, *Rumex acetosella*	45	29	1	
Yellow dock, *Rumex crispus*	45	10	0	
Bitter dock, *Rumex obtusifolius*	23	0	0	
Plantain, *Plantago major*	47	39	7	
Spiny amaranth, *Amaranthus spinosus*	45	34	0	
Rough pigweed, *Amaranthus retroflexus*	40	4	0	
Jerusalem oak, *Chenopodium botrys*	19	0	0	
Lamb's-quarters, *Chenopodium album*	42	33	1	1 doubtful cutaneous; 1 doubtful intradermal
Mexican tea, *Chenopodium ambrosioides*	36	4	0	
Halberd leaved orache, *Atriplex pastula hastata*	28	12	0	
Russian thistle, *Salsola pestifer*	32	14	0	
Western water hemp, *Acnida tamariscina*	50	0	0	
Common hemp, *Cannabis sativa*	30	0	0	
Pickleweed, *Salicornia spp.*	25	0	0	
Rabbit bush, *Franseria deltoidea*	28	0	0	
Greaseweed, *Sarcobatus vermiculatus*	28	0	0	
Tarweed, *Hemizonia spp.*	29	0	0	1 positive cutaneous
Winter fat, *Eurotia lanata*	29	0	0	
Meadow rue, *Thalictrum purpurascens*	28	0	0	
Bastard fever weed, *Parthenium hysterophorus*	31	0	0	
Privet, *Ligustrum vulgare*	34	23	4	1 positive ophthalmic; 1 positive intradermal
Dandelion, *Taraxacum officinale*	29	0	0	
Clover, *Trifolium pratense*	31	0	0	
Rose, *Rosa rugosa*	14	15	0	
Coreopsis, *Coreopsis spp.*	18	0	0	
Daisy, *spp.*	17	0	0	
Poppy, *spp.*	17	0	0	
Wild carrot, *Daucus carota*	16	0	0	
Alfalfa, *Medicago sativa*	31	0	0	
Nettle, *Urtica gracilis*	8	0	0	
Cotton, *Gossypium spp.*	10	14	0	
Cosmos, *Cosmos bipinnatus*	17	0	0	
Cat-tail, *Typha latifolia*	32	0	0	
Mustard, *Brassica nigra*	20	0	0	
Fleabane, *Erigeron spp.*	1	0	0	

Constituents of Commercial Fertilizer and Insecticides.—Wodehouse has been impressed by the tremendous amount of dust that surrounds the fertilizer factories in Alabama, and he has found particles of organic fertilizer constituents on pollen slides. There are two general types of fertilizer manufactured in this region. One is made up

entirely of inorganic minerals, while the other contains such organic materials as cottonseed meal, fish scrap, castor-bean meal, tankage, and bone meal. Some of the factories manufacture fertilizer throughout the entire year, but most of the product is manufactured and sold in the early spring and ceases to be moved after the early part of May. If any of the constituents of fertilizer are responsible for summer hay fever of unknown origin, we would expect to find many cases in the neighborhood of the factories and warehouses. We would also expect to find that cases in the city are more acute in the early spring, with complete relief of symptoms by the middle of May, and that in the rural districts the onset is in the spring with gradual improvement as the rain washes the fertilizer into the soil. Cottonseed meal has been used for routine testing for several years, and in patients sensitive to it, it gives very intense reactions. Although cases of hay fever and asthma due to cottonseed meal have been encountered, the symptoms were not limited to the summer months. All tests with this material have been uniformly negative. The other constituents of fertilizer have been used in testing for a brief period, and only a few tests have been made. The results of these investigations are summarized in Table III.

TABLE III

RESULTS OF TESTS WITH FERTILIZER AND SPRAY CONSTITUENTS

TEST MATERIAL	CUTANEOUS	INTRADERMAL
Constituents of Fertilizers		
Cottonseed meal	44	28
Fish scrap	3	0
Bone meal	2	0
Castor-bean dust	4	0
Tankage	2	0
Constituents of Insecticides		
Cube root	1	2
Derris	0	0
Timbo	0	0
Pyrethrum	44	30

Table III also shows the results of tests with the constituents of insecticides. Pyrethrum has been used almost routinely in testing these patients with negative results, and, at present, investigations with cube root, derris, and timbo are being made.

Insects.—The results of testing with insect scales are summarized in Table IV. The reaction with moth scales was not accompanied by clinical sensitization. The extract of tanytarsus gave 1 positive cutaneous and 3 positive intradermal reactions. This insect is attracted in large numbers to the lights of the hydroelectric dams in Alabama. I have

reported a case* of hay fever due to this insect in which was demonstrated the presence of reagins by passive transfer. The patient was relieved of symptoms when he was away from the dam and throughout the winter season except when exposed to insects removed from the dynamos in the process of cleaning. Treatment with an extract of the tanytarsus gave marked relief of symptoms. I recently encountered two additional cases with positive skin tests and relief with treatment, but there was no history of contact.

TABLE IV

TESTS WITH INSECT PARTS

INSECT	CUTANEOUS	INTRADERMAL	REACTIONS
Tanytarsus	20	38	1 positive cutaneous 2 doubtful cutaneous 3 positive intradermal
Bee	4	0	
Caddis fly	4	0	1 doubtful cutaneous
Mosquito	0	1	
Moth scales	2	4	1 positive intradermal
Butterfly scales	1	0	

Because certain investigators have suspected the privet as the cause of summer hay fever of unknown origin, because skin tests with privet pollen have been negative with one exception, and because many of the patients state that they are worse in the neighborhood of privet hedges, I have been interested in the little white fly which infests these bushes. This insect is the *Dialeurodes citri*, or citrus white fly. These flies make their appearance in April and are quite abundant from May until the appearance of frost. They may be found in large numbers around privet and euonymus bushes, both flying in the air and adherent to the undersurface of the leaves. So minute that they can pass through window screens, they are abundant about indoor electric lights. Their wings are covered by delicate white scales readily wiped off. This insect is distributed over the southeast and infests an area that corresponds very closely to that in which is found summer hay fever of unknown origin (Fig. 2). It is being investigated as a possible cause of this type of hay fever.

Molds and Mildews.—The results of testing with molds and fungi are summarized in Table V. Four hundred and eighty-five cutaneous and 64 intradermal tests were made, and except for one positive intradermal reaction with *Aspergillus niger* and one with millet smut, all were negative. I have had no experience with the following fungi: *Acremoniella*, *Acrothecium*, *Actinomyces*, ergot, *Hyalopus*, *Pilaria*, *Pilobolus*, the polypores, and powdery mildews.

*Published in the International Correspondence Club of Allergy.

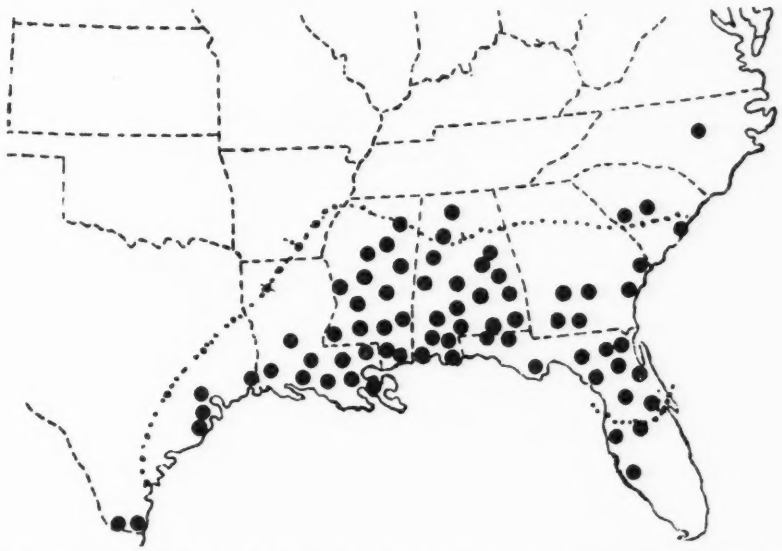

Fig. 2.—Map showing distribution of the citrus white fly and its relation to the area from which hay fever of unknown origin has been reported. The dotted line indicates the boundary of the area of hay fever; the large dots, areas from which the citrus white fly has been reported.

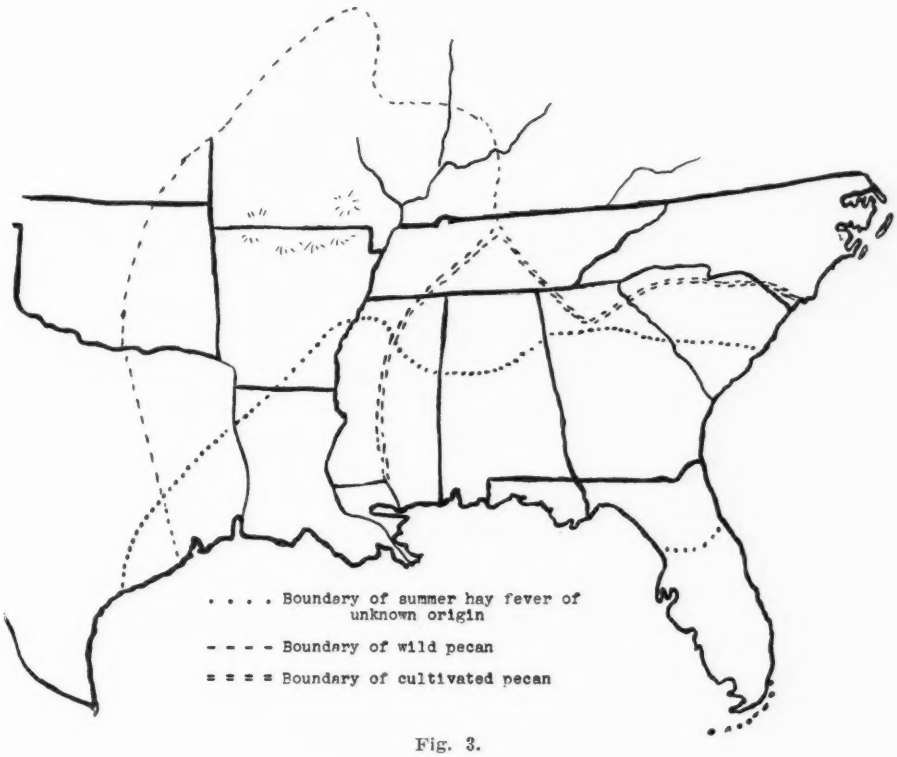

Fig. 3.

TABLE V

RESULTS OF TESTS WITH FUNGI

	CUTANEOUS	INTRA-DERMAL	POSITIVE REACTIONS
Molds and Mildews			
Achorion schoenleinii	5	2	
Acremoniella	0	0	
Acrothecium	0	0	
Alternaria	18	5	4 doubtful cutaneous
Aspergillus flavus	8	3	2 doubtful cutaneous
Aspergillus fumigatus	18	3	4 doubtful cutaneous
Aspergillus glaucus	17	2	5 doubtful cutaneous
Aspergillus nidulans	17	1	3 doubtful cutaneous; 1 doubtful intradermal
Aspergillus niger	18	2	2 doubtful cutaneous; 1 positive intradermal
Cephalosporium	8	3	1 doubtful cutaneous
Cephalothecium	6	2	2 doubtful cutaneous
Chaetomium	18	2	2 doubtful cutaneous
Cladosporium	6	3	
Epidermophyton inguinale	6	1	
Ergot	0	0	
Fusarium oxysporum	5	2	1 doubtful cutaneous
Helminthosporium	8	3	2 doubtful cutaneous
Hormodendrum herbarum	16	1	4 doubtful cutaneous
Hyalopus	0	0	
Microsporum lanosum	4	1	3 doubtful cutaneous
Monilia albicans	22	3	2 doubtful cutaneous
Mucor plumbeus	19	2	2 doubtful cutaneous
Mushroom	0	0	
Oïdium lactis	6	1	
Penicillium camemberti	20	0	2 doubtful cutaneous
Penicillium chrysogenum	21	1	6 doubtful cutaneous
Penicillium digitatum	10	1	2 doubtful cutaneous
Penicillium	18	1	1 doubtful cutaneous
Pilaria	0	0	
Phoma	2	0	
Pilobolus	0	0	
Polypores	0	0	
Powdery mildew	0	0	
Puffballs	6	1	
Rhizopus nigricans	16	2	
Saccharomyces cerevisiae	5	1	1 doubtful cutaneous
Trichoderma koningi	20	1	
Yeasts and Actinomyces			
Actinomyces	0	0	
Baker's yeast	17	2	4 doubtful cutaneous
Brewer's yeast	17	2	1 doubtful cutaneous
Distiller's yeast	17	1	1 doubtful cutaneous
Fleischman yeast	16	1	
Lactose fermenting yeast	12	0	1 doubtful cutaneous
Lager beer yeast	16	1	2 doubtful cutaneous
Smuts and Rusts			
Sporobolus smut	23	2	1 doubtful cutaneous
Ustilago maydis	6	1	
Ustilago zea	2	0	
Ustilago hordei	2	0	

TABLE V—CONT'D

	CUTANEOUS	INTRA-DERMAL	POSITIVE REACTIONS
Smuts and Rusts (cont'd)			
Ustilago avenae and levis	2	0	
Urocystis occulta	2	0	
Tilletia tritici and *levis*	2	0	
Sphacelotheca cruenta	2	0	1 doubtful cutaneous
Sphacelotheca sorghi	2	0	
Millet smut	2	4	1 positive intradermal
Cladosporium effusum	0	0	

The powdery mildews are quite abundant on the leaves of roses, legumes, composites, dandelions, oaks, and crepe myrtles. They are especially destructive to apples, cherries, and other fruits of the *Rosaceae* family and affect the leaves rather than the fruit, forming a white, powderlike covering from May to frost. These mildews are worthy of further consideration as a possible cause of summer hay fever of unknown origin.

Worthy of special attention is the pecan scab *(Cladosporium effusum)*. This fungus infests the leaves and outer shells of the nuts of certain pecan trees, turning them a grayish black. Of the various species of cultivated pecans, the Delmars are most gravely affected, the Schleys almost equally severely, and the Success slightly less. Fig. 3 shows the distribution of cultivated and wild pecans, and it is interesting to note that the cultivated pecan is found exclusively in the area from which are reported cases of summer hay fever of unknown origin. In the case of this fungus, spore formation takes place between May and October. Perhaps its geographical distribution and period of spore formation have no actual bearing on summer hay fever of unknown origin, but the coincidence is worth investigating. At the present time, this fungus is being grown on culture media, and material will be available for testing during the year.

CONCLUSIONS

In the southeastern part of the United States there is encountered a type of seasonal hay fever which begins about May 15 and ends in October. In every respect, this type of hay fever resembles seasonal varieties due to pollen, but skin tests with the pollens of grasses, trees, weeds, and flowers, insect scales, fungi, and the constituents of commercial fertilizer and insecticides have been negative except for one case in which was demonstrated a marked degree of sensitivity to the scale of the tanytarsus and in two others reacting less intensely.

A summary of the tests made in this investigation has been presented, indicating the substances which have been inadequately tested

as well as some which have not been used at all in testing, but which seem to be possible causes of this type of hay fever.

Further investigation of the pecan scab *(Cladosporium effusum)* and the citrus white fly *(Dialeurodes citri)* seems to offer the possibility of solution to this problem representing approximately 10 per cent of all the hay fever encountered in the southeast.

DISCUSSION

Dr. Hal M. Davison, Atlanta.—Being one of the doctors mentally and financially indigent to this area, I am deeply appreciative of the remarkable piece of work that Dr. Weil has just reported. We have been discussing this with Dr. Weil for several years. I have gone over his paper very carefully and attempted to discover something that we might add. I cannot do it. I can only say that in our area around Atlanta there is a very definite percentage of cases such as he describes, perhaps around 10 per cent, but not so large as he has in Montgomery.

These cases show no difference from the other cases which we find sensitive to the grass pollens. We have followed his line of investigation but have not been as thorough. We have exposed slides in an attempt to find something in these patients' homes or the places where they work, but have found nothing that would help.

We have given them pollen extracts such as we do in the fall with the ragweed cases. We have been rather successful in treating some of the cases that occur only in the ragweed season and that give no skin reactions. We begin with large doses of the extract, and some of these patients have gotten better results than those who gave definite skin reactions. That is not true of the above-mentioned cases.

I believe we have not been successful with treatment in a single patient of this type; I have nothing, therefore, to add to his paper.

Dr. Samuel M. Feinberg, Chicago.—Although I do not come from the South, I am rather impressed by Dr. Weil's pessimism about fungi, despite the fact that it seems from his records that he has more reactions to them, even though they are weak reactions. He has more reactions to fungi than anything else.

Now, it is still my hope and my belief that it is possible that he has failed to locate appropriate fungi in connection with that type of allergy.

Just to mention an example of a possibility, I was talking to Dr. Gilman, Professor of Mycology at Iowa State College of Agriculture, some time ago, and I mentioned to him about reactions that I obtained with ergot in yeast-sensitive patients; I said, "Of course, it is of no significance because we are not concerned with ergot. It is only of academic interest because of its belonging to the same family of ascomycetes."

He said, "You are mistaken. Ergot is a common fungus, infesting grasses, and you find it all over."

I mention that as a possibility of a fungus with which Dr. Weil has not worked, and it is rather difficult to obtain a culture of it.

I mention ergot—but there are other parasitic fungi which are difficult to obtain. You cannot get them on the culture plates, and it is hard to obtain them from nautral sources. I would like to beg Dr. Weil not to neglect absolutely or give up his search for possible fungus sources.

DR. HOMER E. PRINCE, Houston.—I want to repeat all that Dr. Feinberg has just said regarding the possible role of mold fungi in these conditions, as Dr. Weil has so ably described. I think Dr. Weil is to be congratulated for suspecting the fungus which he has determined as growing upon the leaves and outer shells of cultivated pecans.

It just happens that in our territory of Houston there are a number of, not cultivated, but wild pecans and various species of hickory, and I would not be surprised if further investigation showed a similar or the same *Cladosporium* on the hickory trees.

Regarding the possibility of fungi in the soil, we have one problem common to the whole district that perhaps does not exist everywhere. The temperature in the South throughout the greater part of the year is quite conducive to the growth of enormous quantities of mold spores, and, naturally, such growth occurs during the damp winter months and the spring; then, when the relatively dry season begins in the late spring and lasts through the summer, the possibility for the dispersion of those spores by the air is perfect.

One fungus particularly, or rather a smut, which grows on Johnson grass, has come to my attention, particularly in our territory. Johnson grass in some years has been subjected to an enormous amount of this smut. I have collected Johnson grass smut, and it is easily available in large quantities; but I will admit we have not found any relationship with clinical symptoms. I shall give Dr. Weil some of our smut extract and would be pleased to know if he can correlate sensitization to it with his clinical symptoms.

DR. B. G. EFRON, New Orleans.—Dr. Weil referred to a survey of early summer hay fever in the South that I made in 1938 by sending a questionnaire to eleven allergists practicing in this region. I shall read only some of the more pertinent findings in this survey.

1. The early summer hay fever season is longer in the more southern section of this region than in the northern part.

2. The concentrations of test solutions used to determine pollen sensitivity are greater in the southern section than in the northern part of this region. For instance, one Houston allergist uses 1:10 pollen solutions intradermally; the Montgomery allergist reported using 1:25 intradermally. In New Orleans we have used as high a concentration as 1:30; whereas, Memphis, which is geographically in the northern part of this region, reported the use of 1:1,000 and 1:2,500 solutions. Ten of the eleven allergists who participated in the survey used both scratch and intradermal tests; the other used intradermal tests only. It would appear, therefore, that the test strengths found adequate in the East and Middle West to elicit skin evidence of pollen sensitivity are inadequate to elicit such sensitivity in the more southernly cities of the South.

3. The incidence of skin test negative cases in early summer hay fever is greater in the more southern cities. The actual percentages reported from these localities are not to be too rigidly interpreted, since the use of such concentrated solutions as those reported from these localities often results in false positive reactions due to the presence of nonspecific irritants.

4. What is the significance of these skin test negative cases? Does it mean that present day grass pollen extracts are not sufficiently potent antigenically to bring out definite reactions in early summer hay fever, or is another, as yet unidentified, allergen responsible for these cases?

DR. WARREN T. VAUGHAN, Richmond.—As I understand it, Dr. Weil wants suggestions, for what value they may or may not be worth. We are just on the edge of his geographic area.

First, in regard to fungi, we do not have the type of case that Weil observes, unless that case is allergic to fungi, and it is fungi that are responsible for trouble in the interseasonal period. It is not always *Alternaria*. We talk a lot about that because we can see it on the slide, but there are other fungi.

I have but one other suggestion which may or may not be of value. I have seen several persons from the region of Savannah and other parts of Georgia who are allergic to paspalum. This is also known as Dallas grass, wayside grass, and roadside grass.

Grubb and I have convinced ourselves that there are species specificities as well as family specificity among the grasses and that this may play a part; in other words, it is not just "grasses."

There are only four positive ophthalmic reactions to paspalum on Weil's list. I do not know whether he tested all of the cases or whether those are just the four that were tested.

The other grass that I would suggest he might be interested in studying is St. Augustine grass, which is a variety of redtop and which we have found to be responsible for some cases in the neighborhood of Jacksonville, Fla.

DR. WILLIAM F. MITCHELL, Columbus, Ohio.—In view of these further suggestions, I wish to add that in central Ohio we also see cases of this type. It has occurred to me in looking at pollen slides that the only thing which varies with the severity of symptoms is the amount of debris on the slide, exclusive of pollen, mold spores, soot, and dust. It seems to me that this debris must come from plants or insects. I have thought of no way to follow out this problem but wish to offer this observation as a probable clue to the question under discussion.

DR. WEIL.—Doctor Feinberg says he still thinks that we have not exhausted the possibilities that fungi may be responsible for our summer hay fever of unknown origin. I am duly appreciative of that possibility and, for that reason, am interested in the possibility that the pecan scab may be of importance. I do not feel that we have exhausted the possibilities so far as fungi are concerned, and I feel that, by cooperation with plant pathologists, we may find other fungi in sufficient abundance to deserve consideration as a possible cause of this type of hay fever.

We have exposed Petri dishes in the homes of our patients during the summer and have grown eighteen or twenty species of air-borne molds, and these have been used for testing. As the results were entirely negative, the species were not identified, and consequently this work was not included in our report.

I congratulate Doctor Efron on having reduced his percentage of cases of unknown origin to such a low figure, and I hope some day to have the pleasure of knowing exactly how he has done it. I am not convinced that his success is due entirely to the method of making extracts, since

it is hard for me to understand why patients should react to 1:1,000 extracts in New York and Philadelphia, yet fail to react to 1:25 extracts in Alabama and New Orleans. The reason why we use such strong extracts is obvious. Because we have failed to get reactions to weaker solutions, we have made them stronger and stronger until we reached a concentration of 1:25. It seems to me that it is a little early in the season to be sure that Doctor Efron will succeed in getting as much improvement following treatment as he anticipates.

Doctor Bernton asked if we had done ophthalmic tests. He will find the results of these tests in our tables. Doctor Vaughan states that Dallas grass differs in its antigenic properties from the other members of the *Paspalum* family. I can neither confirm nor deny this observation, but we have used Dallas grass pollen without positive results. St. Augustine grass has not been used for testing.

I am grateful to those men who have been kind enough to discuss my paper and hope that other allergists will be on the lookout for summer hay fever of unknown origin. Perhaps we will find that the area is larger than we supposed.

MAY FLY (EPHEMERIDA) HYPERSENSITIVITY

KARL D. FIGLEY, M.D.
TOLEDO, OHIO

TO ANYONE not familiar with the annual invasion of the myriads of May flies which occurs each summer in various parts of the United States, especially in the Great Lakes region, their abundance is unbelievable. In attempting to portray this, I can do no better than to quote a passage from a publication by Prof. James G. Needham of Cornell University, "Burrowing Mayflies of Our Larger Lakes and Streams"[1]: "How abundant they are in all our large lakes and streams is well attested by the vast hordes of adults that appear in the air at the times of their annual swarming. They issue from the water mainly at night. They fly away to the banks and settle upon the shore vegetation. They cover the sides of buildings. They fly heedlessly into the faces of pedestrians. They settle upon the stream-side willows until their accumulated weight bends, and often breaks, the boughs. In the streets of riparian cities they fly to lights at night and fall beneath them in heaps upon the ground. Their bodies, crushed under the wheels of cars, render the rails slippery, sometimes impeding traffic. . . . Sometimes they stop the river steamers by clogging the machinery. No dweller by the shores needs to be convinced of their abundance." Figs. 1 and 2, taken at night near Port Clinton, Ohio, which is some forty miles east of Toledo on the south shore of Lake Erie, give some idea of the abundance of these insects.

The May fly belongs to the order *Ephemerida*, named from the Greek word *ephēmeros*, meaning "lasting but a day." Various other names for them are "June flies," "lake flies," "shad flies," and "Canadian Soldiers." They are found along the shores of lakes and large rivers in various parts of the world. Isaak Walton mentioned them in his *Compleat Angler*, and I have seen them on the River Seine near Paris. In North America May flies are found most abundantly in the Great Lakes region, along the Mississippi, around the Finger Lakes in New York State, and among the Wisconsin lakes. The May fly larvae live on the mud bottoms of rivers and shallow lakes and, for this reason, are so very abundant along the shores of Lake Erie with its numerous shallow bays. About eighty-five known species of May flies occur in North America, divided into half a dozen genera. The most common of these are the brown drakes *(Hexagenia)* (Fig. 3). Other well-known species are the yellow drakes *(Pentagenia)* and the beautiful Mackerels *(Ephemera)* (Fig. 4).

In 1929 I reported four cases of hypersensitivity to May fly emanations.[2] Since that time I have routinely tested all patients with seasonal

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hay fever and asthma for May fly sensitivity. In passing, it should be said that the time of the annual May fly invasion of the Great Lakes area is from the latter part of June until the first of August. The onset depends on how early the lake water reaches the proper sustained degree of warmth. It is apparent that the May fly season roughly parallels that of the grass pollens and English plantain, as well as the early mold spore season, thus adding to the complexity of diagnosis in early cases of seasonal hay fever and asthma in the Great Lakes area.

Fig. 1.—May flies on side of building at Port Clinton, Ohio.

In a series of 1,284 seasonal hay fever and asthma patients who were adequately tested, 95 (7.4 per cent) gave positive cutaneous reactions stronger than one-plus to May fly. Of these, 40 patients owed their symptoms all or in part to May fly sensitivity. Twenty of them reacted only to May fly and had no symptoms aside from those during the May fly season. The other 20 reacted only to May fly and ragweed pollen; they did not react to grass or plantain pollen or mold spores. These 40 patients were all treated with extracts of May fly or of May fly and ragweed pollen, and the results were quite satisfactory. In these 40 patients the cutaneous tests to May fly were usually three-plus or four-plus, and in every instance where passive transfer was attempted, the result was strongly positive.

Fig. 2.—May flies expiring after nocturnal mating.

Fig. 3.

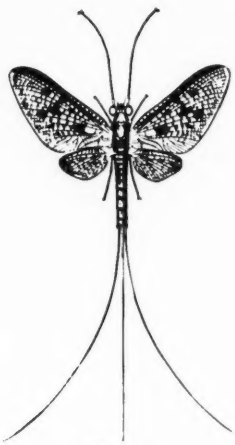

Fig. 4.

Fig. 3.—Adult male May fly, *Hexagenia bilineata.* (After Needham.)
Fig. 4.—Adult male May fly, *Ephemera varia.* (After Needham.)

The question will at once be raised about the other 55 patients showing positive reactions to May fly, and the specificity of their reactions. That they were specifically sensitive is attested by the fact that many of them were tested by passive transfer or by inhalation of powdered May fly; all so tested reacted positively. These 55 patients had all been exposed more than once to May fly contact and had developed specific hypersensitivity; however, they were not treated with May fly because they lived inland and could avoid exposure. In numerous instances, grass pollen sensitivity was more pronounced than May fly sensitivity, so that it was not considered necessary to treat with May fly. Because of the fact that glycerosaline insect extracts may at times give nonspecific cutaneous reactions, no cases were included that did not show at least a two-plus cutaneous test to May fly.

TABLE I

SUMMARY OF CASES

Total cases seasonal hay fever and asthma reviewed		1,284
No. cases giving two plus or stronger cutaneous reaction to May fly		95 (7.4%)
No. cases reacting to May fly only	20	
No. cases reacting to May fly and other seasonal inhalant, usually ragweed	20	
No. cases reacting to May fly but not requiring treatment	55	
		95

The following reports illustrate some of the cases encountered:

CASE 1.—V. E. L., male, aged 34 years, lives in Sandusky, Ohio, and in the summer works on a dredge in Sandusky Bay. He developed seasonal hay fever and asthma at the age of 15 years. Symptoms always begin coincident with the annual May fly invasion. During recent years, asthma has been very severe and lasts until October, and he has been hospitalized several times because of this. He was first seen by me in March, 1938, and gave a four-plus cutaneous reaction to May fly; there were no other reactors. Treatment with May fly extract gave complete freedom from symptoms last summer despite intense exposure to the insects during June and July. The patient is still being treated by the perennial method.

CASE 2.—J. S., male, aged 39 years, resides and works in Toledo, some 5 miles from Lake Erie. He was first seen on May 20, 1936, having severe asthma which had begun three days previously for the first time. The patient stated that he had had some hay fever in the fall of 1935. It was assumed that the patient's asthma was due to grass pollens, but tests with these were negative although he gave strong ragweed reactions. At a second visit, strong reactions were obtained to May fly, and it was then learned that the patient, an ardent yachtsman, had been scraping dead May flies from the hull of his boat just prior to the onset of his asthma. Passive transfer tests gave strong reactions to May fly and ragweed but negative reactions to grass pollens and mold spores. This man has been treated since the summer of 1936 with May fly and ragweed extracts. The result has been complete freedom from symptoms despite frequent exposure to May flies while sailing or working on his boat.

CASE 3.—R. DeM., male, aged 24 years, was first seen on June 15, 1935. The patient stated that since the age of 7 years he had had hay fever every year from August 15 until frost, with some asthma during sultry weather. When first seen he had been having hay fever for the previous two weeks, the first time he had ever had it in early summer. Cutaneous tests gave strong reactions to grass and ragweed pollens and to May fly. This man lives in Fremont, Ohio, some twenty miles south of Lake Erie, but had been accustomed in the summer to spend frequent week-ends at the beaches on the lake shore. Since 1935 he has been successfully treated for his seasonal hay fever and asthma with a mixture of grass and ragweed pollen extract. By remaining away from Lake Erie during the May fly season he has had no trouble from this source.

In the routine testing of the 1,284 cases of seasonal hay fever and asthma, cutaneous tests were always done with caddis fly extract as well as May fly extract. Ten patients gave positive reactions to caddis fly, about two-plus, but at the same time gave stronger cutaneous reactions to May fly. The late Dr. Salvatore Parlato, as is well known, wrote extensively regarding caddis fly *(Trichoptera)* hypersensitivity.[3-6] Since our almost simultaneous publications in 1929, there was always a good-natured rivalry between us as to the relative incidence and importance of May fly and caddis fly hypersensitivity in the Lake Erie region. Shortly before his death, Parlato published a paper on May fly sensitization[7] and in the summary stated that he did not believe the May fly to be as common an allergen as the caddis fly. From my observations over an equal period, I believe the reverse to be true. This divergence of opinion is explainable as follows: Caddis flies are undoubtedly more abundant at the eastern end of Lake Erie in the Buffalo area where Parlato made his observations. They inhabit the clean, sandy bottoms of lakes and streams. The May fly larvae, on the other hand, are burrowers, requiring mud and silt for their existence. This condition obtains ideally in the shallow bays at the western end of Lake Erie, where the water is only a few feet deep, rather than at the eastern end where the water is several fathoms deep. It is true that caddis flies are prevalent at the Toledo end of the lake, but they are so outnumbered by May flies as to be almost unnoticed.

In this study, routine testing was done by the cutaneous or the scratch method. The May fly is a good skin sensitizer, and scratch tests were depended upon to point out clinical hypersensitivity. However, in numerous instances, intracutaneous tests were done with both caddis fly and May fly, and in each case the reactions were usually equally positive by intracutaneous test, although the scratch test to caddis fly might be negative. This finding also was obtained by passive transfer in each instance attempted. Consequently, I believe there is an antigen common to both the May fly and caddis fly, as well as species-specific antigens, but I have not had an opportunity to prove this experimentally.

In order to understand how May flies produce allergic manifestations due to specific hypersensitization, a brief account of their life his-

tory is in order. There are two periods in the life cycle of the May fly: its underwater form, and its brief existence as the adult insect. In its underwater or larval form, the May fly exists as a tiny six-legged creature called a nymph, which breathes through gills and has strong jaws with which to burrow and chew (Fig. 5). During its aquatic existence which may last from one to three years, the nymph undergoes successive moults. After several moults, there appear on the body four little sacs which are the beginning of the wings. With each moult these wing sacs grow larger, until finally on some warm summer evening at the end of the underwater life, the nymph floats to the surface, splits open along the back, and after scarcely a second's pause, the winged May fly emerges (Fig. 6).

Fig. 5.—Dorsal view of nymph, *Hexagenia bilineata*. (After Needham.)

Most of the May fly species go through another moulting after acquiring wings. After flying a short distance to the land or some convenient object, the May fly alights and sheds its skin again, this time a thin layer coming off from all parts of the body, including the wings. This shed skin, known as the pellicle (Fig. 7), is very friable and delicate. When the May flies are swarming, myriads of these pellicles may be seen adhering to walls, screens, posts, or trees, where they have been deposited.

It is this friable pellicle that is chiefly responsible for the production of allergic sensitization. It is easily fragmented by a breeze, so that its particles are carried long distances to be inhaled. Unlike the caddis fly and other insects, the May fly sheds no hairs or scales from its wings, so that it must be particles of epithelial masses from the pellicles which constitute the May fly allergen. This has been proved repeatedly by means of conjunctival and inhalation tests.

The fully developed, winged May fly has but one duty to perform during its brief life—to reproduce its kind. This is done during the flying dance, the most conspicuous event in the life of the adult insect.

In the early twilight the fly comes forth, full-fledged, joins its millions of companions in the swarming mass of insects where the males fertilize the females, which drop their masses of eggs on the water's surface (Fig. 8). The eggs settle slowly to the mud bottom of the stream

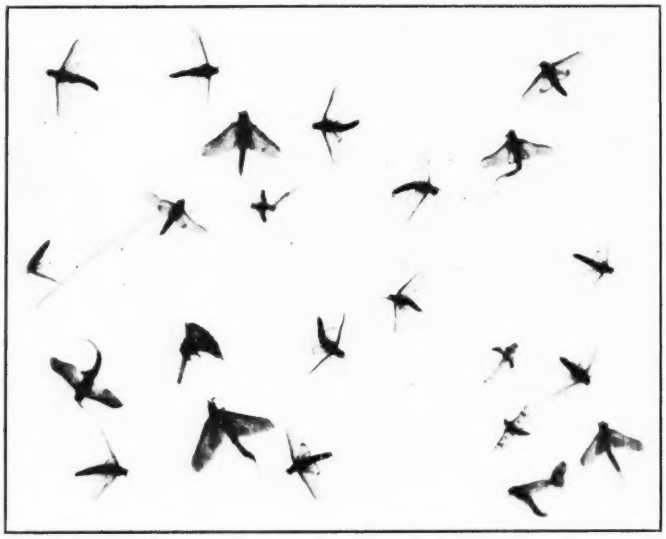

Fig. 6.—Adult May flies in flight.

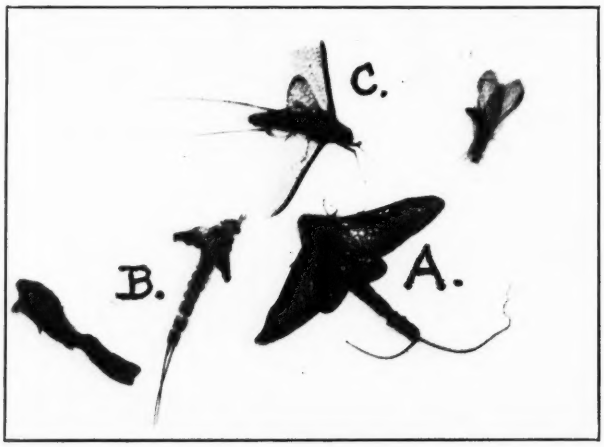

Fig. 7.—*A*, Adult May fly before moulting; *B*, shed skin or pellicle; *C*, fully matured adult insect.

or lake, and a nymph eventually hatches from each to perpetuate the species. Its purpose in life accomplished, the adult May fly dies in a few hours, as it lacks suitable mouth parts with which to take food. Thus it fittingly lives up to its name, meaning "ephemeral," lasting but a day.

Extracts for testing and treatment are made as follows: In the morning adult May flies in any desired quantity are readily scooped up where they have fallen under a light or near the water's edge after their nocturnal mating. They are dried under gauze in the sun for a few days. They are then pulverized in a mortar, washed with some fat solvent, and extracted with buffered saline for 24 hours. My usual stock solution is 3 per cent, or 1:30, and from this are made various dilutions as weak as 1:100,000. The degree of May fly sensitivity and pollen sensitivity is comparable, so that the same precautions are taken when testing or treating with May fly extract. In my experience, treatment of May fly-sensitive patients has been highly satisfactory from the standpoint of relief and prevention of symptoms, possibly because of the specificity of the allergen. Then, too, I have treated a number of patients by the perennial method and have gained the impression that permanent clinical immunity can be brought about in a much shorter time than is the case with perennial pollen treatment.

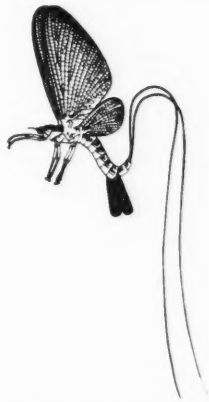

Fig. 8.—Adult female, hovering with egg packets extruding. (After Needham.)

In conclusion, May fly hypersensitivity is quite common among allergically susceptible individuals who are exposed to these insects by reason of residence near the Great Lakes or other large fresh-water bodies such as the Mississippi and the lakes of New York and Wisconsin. Such persons, evidencing symptoms of seasonal hay fever and asthma, should always be tested routinely for May fly sensitization, as this may exist alone or accompany pollen and other seasonal sensitivities.

SUMMARY

The abundance and distribution of May flies are described.

In a series of 1,284 patients with seasonal hay fever and pollinosis who were adequately tested, 95 (7.4 per cent) reacted to May fly. Of these, 20 reacted to May fly alone, and 20 to May fly and some other inhalant, usually ragweed pollen. Three illustrative cases are cited.

A comparison of May fly and caddis fly sensitization at the western end of Lake Erie is given and the opinion advanced that there is an antigen common to both the May fly and the caddis fly, as well as species-specific antigens for both.

A brief account of the life cycle of the May fly and its mode of production of specific sensitization is given.

The method of making May fly extract for testing and treatment is described.

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DISCUSSION

DR. W. W. DUKE, Kansas City, Mo.—The two discoveries, one by Dr. Figley, the other by our friend, the late Dr. Parlato, represent a very interesting advance in the study of allergy. We found in our earlier studies that people could become sensitive to insect bites or stings and react excessively to them. I remember vividly one of my first patients of this sort, a case brought to me in complete shock, with a history of angioneurotic edema, vomiting, and diarrhea to such an extent that he was almost dehydrates. His relief after adrenalin and the oral administration of water containing salt and sugar seemed almost magic.

The type of sensitivity which Dr. Figley describes is of an entirely different nature from the above and reminds one more of sensitiveness to ectodermal substances or other inhalants.

There is an interesting difference between Dr. Figley's fly and Dr. Parlato's fly in that, as the author mentioned, scales of the insect cause the reaction in Parlato's patients, while in Figley's, the excitant is found in fragments of the dried pellicles.

In Kansas City we very seldom have this type of insect allergy. One summer, however, we had almost a plague of scale-bearing flies. I found several cases in this one year. I have had several patients who lived in the Mississippi bottom lands further north than Kansas City.

I have wondered why we do not commonly find grasshopper cases so constantly and in such quantity as Figley finds May flies, but I should think there would be areas where this type of sensitivity to grasshoppers would exist.

I have observed one case of sensitiveness to the common housefly. In this case, the bite of a housefly would cause a delayed inflammatory reaction at the site of the bite. This was followed by a debilitating systemic illness associated with loss of weight if the fly bites were numerous.

This study has added an important chapter to our knowledge of allergy, and in areas where insects prevail at certain seasons, it should solve the source of many cases of nasal and bronchial allergy which would otherwise remain a mystery.

Dr. Samuel M. Feinberg, Chicago.—Even in Chicago we have had some experience with May flies. One or two of our patients have come from outside Chicago.

I should like first to ask Dr. Figley one question: How far inland may we expect to have trouble?

Then I should like to call attention to the fact that in part answer to Dr. Duke's question, I think we cannot expect grasshoppers and similar insects to cause allergic reactions because most of these insects do not have anything in the way of scales or hairs or moulting of a type that Dr. Figley has described; in other words, there is nothing much that can get in the air to be inhaled into our respiratory tracts.

These emanations are apparently applied to the *Ephemerida,* the *Lepidoptera* (butterflies and moths), and the *Trichoptera,* of which the caddis fly is an example. We are likely to be led astray unless we look at the thing from the biologic standpoint.

Also I should like to ask Dr. Figley this hypothetical question concerning the relationship of these flies or insects antigenically. He talked about the caddis fly. What about the butterfly and moth, and what about silk? We obtained a slight impression clinically that some of these fly cases inter-react with silk.

To cite an example briefly: a young man who has seasonal symptoms, eye symptoms, apparently allergic, from year to year in the summer, gave a very marked reaction to silk on scratch test. I could not correlate this thing at all until I began to test with butterfly, moth, May fly, and caddis fly extract, and I also got a reaction to these insects.

I should like to ask one question for information. In Chicago we have used May flies that we caught under lamps and extracted them. Of course, they are through moulting at that time, and I wonder whether Dr. Figley tries to get them before they shed their pellicle in order to get a better extract or whether he gets it from the adult fly.

Dr. Robert L. Benson, Portland, Ore.—Dr. Figley and Dr. Parlato have both demonstrated very nicely that the inhalant effects of insects are examples of true allergy of the type which Coca and Walzer and their associates have designated atopy, and, of course, they get universally good passive transfers.

This is quite different with the bites and stings of insects, which produce a different type of reaction. The essential reaction with these bites and stings occurs within 24 to 48 hours, and, as one would expect, the passive transfer is either absent or very difficult to get with these biting and stinging insects.

I have, on certain occasions, obtained a passive transfer with the biting and stinging insects, but more often it has failed. This demonstration of both Dr. Figley and Dr. Parlato, I think, is valuable not only for its practical benefit but also for bringing out this principle.

Dr. Howard Osgood, Buffalo.—Dr. Parlato really should be here to speak on this; his untimely death was certainly tragic. I test always with May fly and caddis fly and also with silk. Like Dr. Figley, we

often find reactions to both caddis fly and May fly, but not invariably, so that the antigen cannot be identical. I would also corroborate Dr. Feinberg's remarks that we find not infrequently reactions to silk in such individuals. My impression is that, being in the midst of an insect district, as you might say, we are dealing with individuals who are sensitive to a group of insects, very much as we find sensitivity to a group of cereals, for instance, in skin testing with foods.

I think it might be interesting if Dr. Figley made up his dilutions on a protein nitrogen basis, because the protein constituent of extracts of these different insects varies quite widely.

Dr. Milton B. Cohen, Cleveland.—When two equally good men, Dr. Figley at one end of Lake Erie and Dr. Parlato at the other, disagree on the relative importance of two flies, it behooves one of us who lives just halfway between to comment on the relative importance of the May fly and the caddis fly.

I see not nearly as many May flies around Cleveland as Dr. Figley sees up in his territory. Most of the clinical cases of May fly sensitivity I see come from the lower end of the lake, and the only ones I have ever seen that were May fly, and May fly alone, came from the Lakeside or such area around the end of the lake, with the shallow water that Dr. Figley has described.

In Cleveland I have never seen a case that I could say myself was a pure case of caddis fly sensitivity. I do not know—they certainly must exist; but, since I do get reactions to caddis fly and May fly simultaneously, and since the patients that I have whom I suspect of having difficulty are exposed to many more May flies than caddis flies, I have simply concluded without any experimental evidence that these May fly cases are just May fly cases. I have treated them with May fly extract, and good results follow treatment.

Dr. Leon Unger, Chicago.—The other day I met a physician from Keokuk, Iowa, who told me about a whole series of very interesting cases. This man has done some work on allergy and has skin-tested a lot of patients who come from a power plant near Keokuk. He said that all up and down the Mississippi River where they have these power plants they have swarms of flies which they call "river flies." I do not know what "river flies" are, and I am asking for information.

He said they sweep up bushels of these flies at the power plants, and that almost every worker sooner or later becomes sensitized to these flies and develops rhinitis or bronchial asthma, very severe bronchial asthma in a good many cases.

This physician has made extracts of these "river flies" and injected them into the patients, and he claims to get splendid results.

Dr. Clarence K. Weil, Montgomery.—Since the "river fly" has been mentioned, I want to speak briefly of another insect which actually may be the same one. On the hydroelectric dams in Alabama is found a genus of midges, belonging to the family *Chironomidae* and known as the tanytarsus. They are so abundant that they can be gathered easily by wiping off the lights or sweeping the floor. We have had one patient who gave a positive reaction both by testing and passive transfer tests and excellent results following treatment. One winter the patient returned to the dam and remained free of symptoms until he cleaned a

dynamo to which were attached large numbers of the dead insects. As this case will be discussed in more detail in my paper, I shall limit the discussion simply to mentioning the possible importance of this insect. The citrus white fly may also be of importance in causing allergic symptoms.

DR. FIGLEY.—With reference to Dr. Feinberg's question as to how far inland these flies may cause trouble—as the map will show, Toledo is situated at the lower end of the Maumee River, or the beginning of the Maumee Bay, which is about five miles inland from the lake proper. Those persons, whom Dr. Cohen mentioned, who live on the shores of Maumee Bay and farther east along the lake shore toward Cleveland are definitely exposed.

Most of the patients that I see come from Port Clinton and Sandusky. Strange to say, we do not have many cases in metropolitan Toledo itself because it is some five miles from the lake. Many patients who do come from Toledo, as a rule, live on the shores of Maumee Bay.

I have had one or two patients who have lived in town and, without ever seeing these insects, have had definite seasonal hay fever symptoms. On the other hand, when a strong northeast wind carries these insects inland, people living 20 and 30 miles back from the lake are affected. Also I saw May flies once as far south as Lima, Ohio, 70 miles away.

Dr. Feinberg, as to the relationship antigenically between moths, butterflies, etc.—these cases I have reported have all been tested with moth or butterfly extract, and I have failed so far to get a reaction.

Dr. Feinberg also inquired whether the extracts were made from the pellicle or the adult fly. It is much easier and better to make the extracts from the adult fly because the pellicles are rather difficult to collect. You have to pick them one by one from posts; furthermore, the pellicle contains only about one-tenth the nitrogen that an adult fly does. There is plenty of antigen in the pellicle to cause trouble, but I did not bring out that these May flies live only from 36 to 72 hours. After the adults die, they dry very rapidly, and their dried fragmented bodies add to the total amount of epithelial scales in the air.

Doctor Unger inquired whether the so-called "river flies" so prevalent at Keokuk were the same as May flies. They are one and the same. The Bureau of Fisheries has long been interested in May flies because their larvae constitute a major part of the diet of the fish in the Great Lakes and the larger rivers. Professor Needham's outstanding study, "Burrowing Mayflies of Our Larger Lakes and Streams," made for the Bureau of Fisheries years ago was based on material obtained mainly from the Mississippi dam at Keokuk.

THE USE OF POTASSIUM CHLORIDE IN THE TREATMENT OF ALLERGIC CONDITIONS

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THE publications on the use of potassium chloride in the treatment of allergic conditions[1, 2] have stimulated much interest in the drug's use, both on the part of members of the medical profession and of the lay public because of the great publicity it has received in medical journals and the lay press. For this reason, it seemed advisable to attempt an evaluation of its usefulness. The cases selected for this study were in a group of patients under treatment for ragweed hay fever and allergic coryza in the Allergy Clinic of the Post Graduate Hospital and in private practice.

A total of forty-three cases was observed, of which thirty-one were suffering from ragweed hay fever and twelve from nonseasonal allergic coryza. Of the pollen cases, fifteen were treated with potassium chloride alone, and sixteen, with potassium chloride in addition to the usual phylactic specific injection therapy. Ten of the sixteen patients were treated altogether phylactically, while the remaining six had very brief preseasonal treatments, having been given injections twice a week for from one to three weeks prior to the onset of the season. The twelve cases of allergic coryza were given potassium chloride as an adjunct to the usual immunologic procedures. Serving as controls for the ragweed cases were fifty patients who received the standard pollen injection therapy with no added potassium therapy. All of the hay fever cases studied gave a definite seasonal history of symptoms from pollens for two or more years, and these were carefully classified by intracutaneous tests with varying dilutions of ragweed extract to determine the presence and the degree of sensitivity to the pollen.[3] This classification was verified in each patient by subsequent retesting. Treatment was given according to the degree of sensitivity.

The cases of allergic coryza studied were, as far as could be determined, purely hypersensitive with allergic backgrounds and positive intracutaneous tests, and with no demonstrable active focus of infection in the upper respiratory tract.

PROCEDURE

The patients with hay fever, with the exception of the controls, were given either a solution of potassium chloride or capsules containing the salt, with instructions to take the prescribed amount dissolved in

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a glass of water. The doses administered ranged from 15 to 50 gr. daily. No gastrointestinal symptoms were noted, save in one person. Every patient was seen at weekly intervals by the same investigator, at which time notations were made as to the symptoms and the regularity of medication. The potassium chloride was furnished by the investigator, who was thus able to check carefully the amount of medication taken by each patient.

The fifteen patients treated with potassium chloride alone were not apprised of the fact that their treatment was in any way different from the standard injection therapy used in the hay fever clinic. Therefore, in addition to the potassium chloride, each of these cases was given graduated weekly injections of physiologic saline solution in order to create the impression that he was receiving injection therapy of a type similar to that of the rest of the clinic patients. This was done in an attempt to remove the psychic element.

Sixteen cases received the standard phylactic injection therapy of an alkaline-saline ragweed extract and were treated three times weekly in doses according to their classification and degree of sensitivity. Ten of these received treatment following the onset of the season, while six had had the advantage of from one to three weeks of preseasonal therapy in addition. All received potassium chloride and were observed similarly to those who were treated with potassium chloride alone.

Fifty control cases received standard weekly preseasonal injection with alkaline-saline ragweed extract in doses according to the classification and degree of sensitivity. They were seen by the same investigator at weekly intervals to determine the effectiveness of the treatment.

All of the patients received the same adjunctive measures for local relief, including cocaine-epinephrine eyedrops, shrinking solutions for the nasal membranes, and ephedrine or propadrine orally.

Every effort was made to establish the allergic coryza cases as truly hypersensitive. A thorough investigation was made for the presence of clinical hypersensitiveness in the past and present history of not only the patient, but of the antecedent and collateral members of his family. There were a thorough physical examination and complete intracutaneous testing with the various allergic excitants, i.e., pollens, inhalants, and foods. Each of these cases demonstrated positive skin reactions, verified upon retest. The chief excitants found positive were house dust, orris root, and dog, cat, goose, and horse epithelium. In addition, these cases were studied in the nose and throat department where the possibility of the presence of active infection of the upper respiratory tract was eliminated. Other diagnostic procedures such as blood counts, determination of sedimentation rates, and x-rays of the sinuses were obtained in a further effort to establish that these

cases were not infective, but allergic, in origin. All the patients had been treated with the standard immunologic procedures during a control period before potassium chloride was administered. During the observation period they were treated similarly, but with the addition of potassium chloride.

RESULTS

The effect of potassium chloride medication in this study was disappointing. Of the fifteen patients with hay fever who received potassium chloride alone, twelve obtained no relief whatsoever from their hay fever symptoms which began in mid-August and lasted through September. Not only was the date of onset not delayed, but the severity of symptoms persisted unabated. Careful questioning revealed that, as far as the patients could determine, no lessening of their symptoms had been obtained at any time. Of these, two continued in great discomfort well beyond the end of the ragweed season into the latter part of September, due, in all probability, to the development of an upper respiratory infection. Thus, a total of twelve cases (80 per cent) of the number investigated had a poor result. Of the remaining three cases, one had a fair result, being better than he had been during the previous season with phylactic injection therapy at this clinic; the second was better than during the previous season when no treatment was given. The third case cannot be considered reliable, for he claimed "weakness" for forty-eight hours following a number of the saline injections and therefore discontinued both the potassium chloride medications and the injections on September 5.

Of the sixteen patients to whom phylactic and incomplete preseasonal pollen injections, as well as potassium chloride, were given, five (31 per cent) continued to have hay fever throughout the season; four (25 per cent) reported immediate definite relief, with a few (less than five) severe days throughout the season; and five (31 per cent) reported considerable relief with only moderate hay fever through the remaining part of the season. Thus, a total of 69 per cent of the pollen-treated patients had satisfactory results, and 31 per cent had poor results. Of the fifty cases in the control group who received a complete series of standard pollen injections, twelve (24 per cent) had five or more days of severe hay fever, nineteen (38 per cent) had fewer than five severe days, and the remaining nineteen (38 per cent) had no severe days.

Of the twelve patients with allergic coryza, only three reported any definite relief of symptoms with the addition of potassium chloride to their routine treatment. These three also noted periods of exacerbation of symptoms when taking potassium chloride. Thus, nine cases (75 per cent) had absolutely no relief from the potassium chloride, while three cases (25 per cent) had very questionable relief.

DISCUSSION

In April, 1938, Rusk and Kenamore[2] reported excellent results in the treatment of six cases of urticaria with a high protein, low sodium, acid-ash diet with added potassium chloride. Their work was stimulated by the recent experimental and clinical publications regarding the effect of potassium on skin and muscle irritability and by the relation of potassium, sodium, and calcium to tissue edema. At a later date, Rusk, Weichselbaum, and Somogyi[4] published a rather extensive report in which they demonstrated that there was an alteration in the blood serum potassium levels in patients suffering from acute and chronic urticaria and bronchial asthma. They believe that, because of electrolyte imbalance, there is a high rate of exchange of potassium from the tissue to the circulating blood, causing an increase in the potassium level of the blood serum and increased tissue irritability because of the low tissue potassium content. They further showed that certain cases with urticarial lesions and asthmatic manifestations had relief of symptoms following the administration of potassium chloride. This was assumed to be due to the availability of more potassium ions in circulating blood. Cohen,[5] in a series of cases, has been unable to verify the clinical results in the treatment of urticaria.

Bloom, in 1938, published the result of his work on the clinical use of potassium chloride in hay fever, sinusitis, and nasal allergy, stating that excellent results had been obtained from its use. In a later publication by the same author,[6] the results obtained in the hay fever cases treated with potassium chloride were practically identical with those previously reported. Many failures were noticed in other allergic conditions, however, especially asthma. The various nasal and skin allergies were described as showing some appreciable improvement with potassium therapy. In some of the cases he found that higher doses of potassium were needed at times to procure relief.

Abt reported satisfactory and even striking results from the administration of potassium chloride in a series of twenty-seven patients, of whom four were stated to be suffering from hay fever, nine from hay fever with asthma, six from allergic rhinitis, and eight from sinusitis, all presumably living in the Chicago area. No description is given by him as to the methods used in the identification and classification, nor is any attempt made to enumerate the excitants found positive by test. The fact, however, that Abt attaches importance in the treatment of hay fever to any therapeutic procedure initiated no earlier in the fall than October 31, renders doubtful the correctness of his observations, generally.

CONCLUSION

Potassium chloride, in our hands, has been altogether disappointing in the treatment of hay fever and allergic coryza.

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Special Reports

EPINEPHRINE HYPERSENSITIVITY

Report of Two Cases

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IN THE Allergy Clinic of the Louisville City Hospital, we have noted the development of necrotic areas in the skin of two asthmatic negroes, at the sites where epinephrine had been injected repeatedly. Similar necrotic areas are not uncommonly observed in patients receiving hypodermic medication and are usually attributed to infection or chemical irritation. In the two patients observed by us, however, we were able to demonstrate that the necrotic areas were due to a definite tissue sensitivity to epinephrine.

In the literature there are a number of reports of idiosyncrasy following the injections of epinephrine preparations. In some of these, the authors reported general and sometimes fatal reactions, and in others, extensive sloughing of tissues. Often the epinephrine was used in combination with a local anesthetic and it is possible that substances other than the epinephrine were the cause of the reaction. In no instance, however, do we find reference to the type of dermal sensitivity such as we observed in our patients.

A somewhat similar condition has been observed following the injection of insulin.[1] Joslin,[2] however, observed but four instances of abscess formation from insulin in the thousands of diabetic patients treated. One case he described as occurring in the hospital "in a negro whose skin was most sensitive to insulin." He said, "Presumably they [abscesses] were due to the tricresol used as a preservative rather than to the insulin."

Halle[3] reported his experiences with the use of epinephrine over a period of eighteen years. In one instance, the administration of one drop of a 0.1 per cent solution of epinephrine mixed with 2 or 3 c.c. of 0.5 per cent solution of procaine hydrochloride used in a plastic nasal operation was followed by excessive paleness of the skin the day of the injection. The following day there developed chills and fever, which was explained by necrosis of the skin under the adhesive dressing. The necrotic area reached the size of a dime on the right side, and was twice as large on the left. A second operation was necessary in order to correct the extended defect of the skin.

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A similar case was observed in a young girl. The anesthetic solution was injected into the skin of the supramaxillary branches for an operation on both accessory sinuses, and a circumscribed necrosis gradually resulted at the site of injection.

In two additional cases of intranasal operations, sloughing and perforation followed the injections.

Cases also were observed in which spasmodic sneezing (from 50 to 100 times) developed after the introduction of epinephrine into the nasal duct, either with a tampon or with a spray.

Symes-Thompson,[4] reported "Idiosyncrasy to Adrenalin With Reference to Its Employment With Local Anesthetics and in Goetsch's Test for Hyperthyroidism." Apparently, the author felt the idiosyncrasy in his cases was due to toxic manifestations of the drug, although he suggests that it is preferable to use a synthetic adrenalin rather than the natural product.

Brown and Barlow,[5] Heinicke,[6] and Lamson and Chambers[7] reported three cases. In the report by Lamson and Chambers,[7] as well as in most of the others which we were able to find in the literature, it is not clear whether the tissue injury was due (1) to an acquired hypersensitivity to epinephrine, (2) to the vasoconstrictor action of the drug and resulting prolonged anemia of the tissues, (3) to the toxicity of epinephrine per se, (4) to pressure necroses of large amounts of fluid injected with the drug, or (5) to the irritative effect either of the epinephrine, preservative, or buffer in the epinephrine solution.

CASE REPORTS

CASE 1.—E. M., a colored female, aged 26 years, had suffered from intrinsic asthma since she was 11 years of age. In 1932 she began to inject herself with epinephrine and noted no untoward results from such administrations until April, 1938. At this time, she noted that a swelling would form at the site of injection about thirty minutes after the administration. This would gradually subside, but in from four to seven days an ulcerated area about 1 cm. in diameter would appear. This inflammation subsided after some days, leaving a darkly pigmented area. This phenomenon would occur despite most careful aseptic technique in the administration of the epinephrine.

On examination, these pigmented areas were found on both arms and thighs, sites where she had received injections of epinephrine (Fig. 1). There was an erythematous eruption on the patient's back which a consulting dermatologist considered a fixed eruption due to phenobarbital. The patient's blood Wassermann and Kahn tests were negative.

Cutaneous lesions were distributed over the anterior and lateral aspects of both thighs, the anterior, lateral, and posterior areas of both upper arms, and the shoulders. There was no suggestion of grouping or confluence in the readily accessible areas. Each lesion was clear-cut and distinct and was dependent only upon the injection of epinephrine.

The necrosis following the injection of epinephrine was due to local tissue anaphylaxis (Arthus' phenomenon). This reaction takes place in an immune

animal and is the attempt on the part of the defensive mechanism to destroy the antigen at the site of injection.

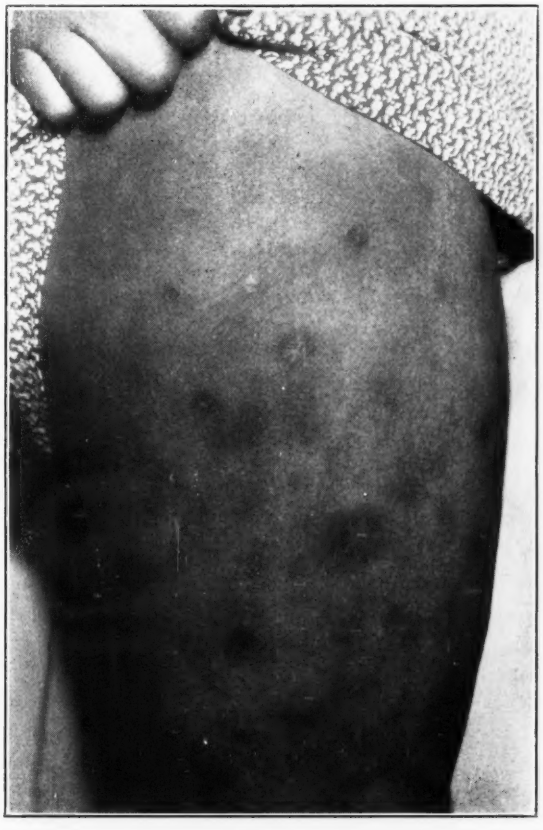

Fig. 1.

It should be mentioned that the epinephrine has not afforded this patient satisfactory relief. The preparations mentioned as causing necrosis have little or no effect on either the pulse rate or blood pressure; it is not uncommon for this patient to take from 10 to 12 injections of 0.5 c.c. epinephrine in a period of two hours in an effort to relieve an asthmatic attack. This case is not one of status asthmaticus since single small doses of synthetic epinephrine hydrochloride (Winthrop) give prompt and efficient relief from an attack. The injection of this preparation, however, produces no skin lesions.

In the course of the frequent self-administered injections that this patient makes, she occasionally injects a small blood vessel unintentionally. Following such administration an interesting phenomenon takes place. Not only do the usual reactions of intravenous epinephrine follow, but previously injected sites (subcutaneous), if not entirely healed over, flare up and pain considerably, often making walking unbearable (Schwartzman phenomenon).

CASE 2.—I. W., a colored female, aged 39 years, had suffered from asthma since infancy. She showed positive skin tests to ragweed, cocklebur, lamb's-quarters, sorrel, feathers, house dust, and to egg, milk, wheat, orange, and potatoes. In 1928 her record showed a four-plus blood Wassermann reaction, and she received treat-

ments for syphilis. The blood Wassermann has been repeatedly negative since 1931. A hysterectomy, salpingectomy, and appendectomy were performed in 1937. An interne's notation in 1939 states, "Asthmatic of long standing—on ward six times in the past year. On several occasions ether-oil enemas were required to control her severe dyspnea."

On examination, pigmented areas were found identical to those reported in Case 1. Sections of the tissue removed from the pigmented areas in both cases showed fibrosis, but there was nothing else not characteristic of ordinary secondary healing of a necrotic area in the skin.

Both cases showed characteristic necrosis following the subcutaneous and intradermal injections of 1:1,000 solution adrenalin (Parke, Davis), 1:1,000 solution epinephrine (Armour), and adrenalin in oil. Neither case showed sensitivity to synthetic epinephrine hydrochloride solution 1:1,000 (Winthrop). This latter solution contains both sodium bisulfite and chlorbutanol as preservatives. Neither case showed necrosis to injections of 0.5 per cent chloretone or 0.1 per cent sodium bisulfite, the preservative and stabilizer used, respectively in both the Parke, Davis and Armour epinephrine preparations.

Both cases gave negative skin tests to beef and pork extracts. Natural suprarenalin is usually obtained from beef suprarenal glands. Patch tests to solutions and crystals of epinephrine, sodium bisulfite, and chloretone were negative.

Passive transfer tests made on three individuals with the serum from Cases 1 and 2 were negative. Injections of adrenalin crystals suspended in saline solution caused necrosis in the skins of both of our patients, but did not cause necrosis in the skins of normal controls. Injections of more concentrated solutions of both chloretone and sodium bisulfite caused irritation and sloughing in the skin of both our patients and in the normal controls.

Interfaced precipitative tests against serial dilutions of adrenalin crystals, sodium bisulfite, and chloretone with blood serum from both cases were negative.

CONCLUSIONS

A number of case reports of epinephrine hypersensitivity appear in the literature. Most of these deal with extensive sloughs, resulting possibly from the vasoconstriction and anemia of tissues, from pressure necrosis, or from toxic effects of anesthetics found in the epinephrine solution. Others deal with the untoward general effects from injections of epinephrine in particularly sensitive individuals.

We have reported two cases in which there appeared a definite acquired tissue hypersensitivity. No reagins could be demonstrated in the sera of either patient by passive transfer tests or by interfaced precipitative tests.

Case 1 is extremely interesting because of the high degree of immunity which the patient has developed to the usual epinephrine preparations. Her immunity is so great that the defensive mechanism walls off the antigen (epinephrine) at the site of injection, and, as an end result, she obtains little or no relief. Synthetic epinephrine, however, gives this patient prompt and efficient relief with no resulting local tissue necrosis.

We have been unable to find in the medical literature reports of similar cases of tissue hypersensitivity.

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CATALPA AS A CAUSE OF HAY FEVER

A Case Report and Results of 84 Skin Tests

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CATALPA has not been reported as a cause of hay fever. This report is made to add catalpa to the list of recorded allergens and to illustrate the potential importance to the individual of environmental pollens which do not fulfill the five postulates of Thommen[1] for the production of epidemic or endemic hay fever.

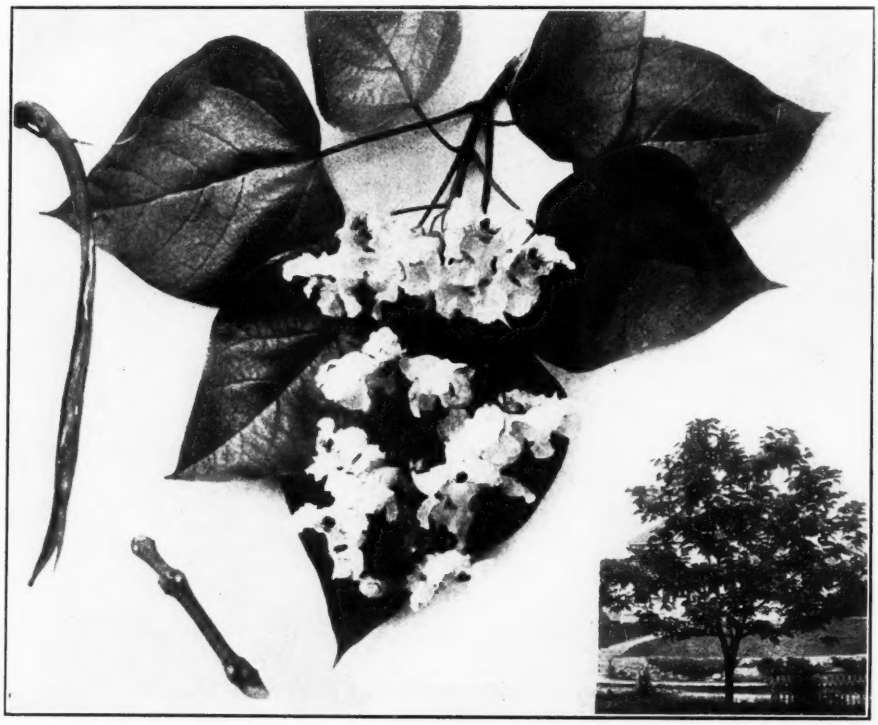

Fig. 1.—Eastern Catalpa, Indian bean. (Rephotographed from Emerson, A. I., and Weed, C. M.: *Our Trees and How to Know Them*, Philadelphia, 1918, J. B. Lippincott Co., p. 282.)

The catalpa,[2, 3] which belongs to the species *bignoniaceae*, is also called Indian bean or Indian cigar (Fig. 1). It is deciduous and hardy, and grows rapidly in any good soil. It is popular for lawn and avenue planting, especially where formal or exotic effects are desired. They are ornamental shade trees with large long-stalked heart-shaped pale green leaves

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and showy terminal clusters of white or pinkish bell-shaped spotted, pleasantly scented flowers which appear in the late spring. The flowers are followed by long slender beanlike pods. There are six species in this country, some of which are native and some of which have been imported from the Orient. The two most often seen are the *Catalpa bignonioides* and the *Catalpa speciosa*. The *Catalpa bignonioides* is native to the South but is cultivated in the northern cities. The bark is silver gray. The wood is light and fine and useful in cabinet work. The *Catalpa speciosa* to which the patient was exposed is larger, hardier, and found abundantly from Indiana to Tennessee and through Arkansas and Missouri. The bark is thicker. The flowers are less conspicuously spotted and are tinged with violet or purple. In rich lowlands it grows fast and is used for railroad ties and posts in the Middle Southwest.

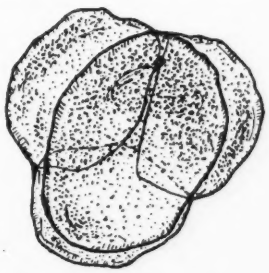

Fig. 2.—Catalpa pollen, 50 to 60 microns. Camera lucida drawing. High power ×700.

The pollen (Fig. 2) is found in the anthers of the bloom. It averages about 50 to 60 microns in diameter. It is interesting that no mention of the pollen was found in any of the standard works on trees.

The Paulownia or princess tree is commonly mistaken for the catalpa because its leaves are very much alike. The bloom of Paulownia is lavender, and the petals are coarse and velvety. Instead of the long bean pods of catalpa, the Paulownia bloom is followed by conical clusters of about fifteen hickory-nut-sized capsules which empty their seed to the wind and remain attached to the tree all winter.

CASE REPORT

A white male, aged 59 years, was first seen in 1930, complaining of ragweed hay fever, migraine, multiple food idiosyncrasies, and some muscular aches and pains apparently relieved by removal of focal infection, all for many years. He had multiple scratch reactions from 1930 to 1931 to vegetables, fruits, nuts, cereals, fish, condiments, epidermals, trees, grass, plantain, ragweed, corn, and cocklebur. He had been moderately light sensitive for years, requiring dark glasses to prevent conjunctivitis in bright lights. Perennial ragweed treatment, begun in 1931, proved so successful it was stopped in 1936, but it had to be resumed in 1938 when symptoms returned.

In May and June of 1935, he had mild but definite hay fever for five weeks. He thought the hay fever was significantly worse when he passed by a long avenue of catalpas early in June of that year. Catalpas were outside his office windows.

He noticed that his symptoms became worse when he opened his windows and that with his windows closed he would have much more comfortable days.

In June, 1936, the catalpa relationship was noticed again. Occasional episodes of transient hay fever were treated with grass and plantain pollen extracts, 1:5,000, coseasonally, with fair results if he avoided the direct exposure to catalpa.

In late May and early June of 1937 the relationship between catalpa and his symptoms became even more evident. On the days when he walked past the avenue of catalpas he would have violent sneezing by the time he got to his office. On the days when he walked a different route and did not have such intimate contact with the catalpas, his symptoms would be very much less. This was observed throughout the pollen season of that tree and subsided promptly after the bloom left.

The same thing was noted to a greater degree in the spring of 1938.

In the fall of 1938, when the perennial ragweed treatment was resumed, treatment with catalpa pollen extract was started. Perennial catalpa treatment, reaching a preseasonal dose of 0.3 c.c. of a 1:33 extract, has increased his tolerance to gross catalpa exposure to a degree which permits him to walk past a group of 75 to 100 consecutive trees in full bloom, with only slight conjunctival irritation. A few daily coseasonal injections of the catalpa pollen extract when they first came into full bloom, about May 15, were followed by perhaps 95 per cent relief. The last bloom was noted on the trees he was exposed to on June 8, and by June 11 every trace of hay fever had gone. In order to avoid confusion in interpreting results of the catalpa therapy, no grass and plantain injections were given before or during this period of symptoms.

Skin and passive transfer tests were strongly positive for catalpa. They were also positive for grass, plantain, and ragweed. The controls were negative.

DISCUSSION

We, together with Dr. David Pipes, of Richmond, tested 86 other patients who had their chief symptoms during April or May with catalpa pollen extract. Of these, 64 were negative or doubtful, 13 reacted weakly but definitely, and 9 had strongly positive reactions. No etiologic significance of the catalpa could be established in any of these patients. In spite of this, the presence of strong reactions in 9 of 86 patients with tree hay fever suggests that catalpa is of importance potentially as a cause of hay fever. It does not seem, in the case presented, to cause trouble at a distance greater than 40 to 50 yards. Pollinating as it does during the season when grass and plantain are at their peak and when most of the trees have completed their pollination, it is recommended that patients not doing well on grass and plantain management be investigated for catalpa hypersensitiveness.

This instance of hay fever from a flowering tree suggests that all seasonal hay fever cases, not relieved by current methods of treatment, should be investigated for sensitization to the flowering plants and trees of their environment. To lend support to this suggestion 100 routine office histories of patients with pollen hay fever were reviewed. Twenty-five of these patients gave histories of transient hay fever from the following environmental flowering plants: marigolds seven times; zinnias and roses four times; clematis, cosmos, and daisies three times; dahlias and privet twice; narcissus and coreopsis once; and unspecified house flowers six times.

SUMMARY

1. A case of hay fever from catalpa is reported.

2. Nine of 86 patients with spring hay fever who were tested had strong reactions to catalpa pollen extract.

3. This and other evidence is offered to point out the potential importance to the individual of flowering plants and trees as causes of hay fever.

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CONTACT DERMATITIS FROM THUROWORT (EUPATORIUM ALTISSIMUM)

Report of a Case

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THE work of Brown, Milford, and Coca[1] laid the foundation for the study of contact dermatitis in relation to the dermatoses which occur as a result of pollen contact. They were able to show that the dermatitis was not due to the atopic substance but to the oil itself. In subsequent

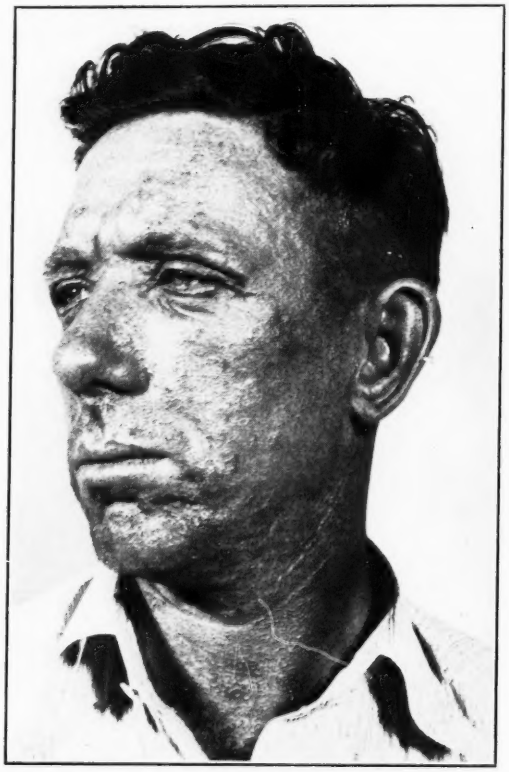

Fig. 1.—Photograph showing the condition of the face when the patient was first seen.

work, the same authors[2] extended and confirmed their preliminary report. The nonatopic oil fractions of the various excitants are obviously not limited to the pollen but are, as shown on numerous occasions, found in the leaves, stems, and flowers. Furthermore, the list of materials from which these oils are obtained is extensive. Fortunately, the history given by the patient was of some help in making an etiological

diagnosis. In so far as we have been able to ascertain, there has been no report of sensitization to the ether-soluble portion of the flower of *Eupatorium altissimum*.

CASE REPORT

E. O. S., male, aged 39 years, was referred with the following history. The onset of the present condition started five years previous to his first visit on Sept. 15, 1935. At the onset the patient noticed a burning, itching, and swelling of his

Fig. 2.

Fig. 3.

Fig. 2.—*Eupatorium altissimum.*

Fig. 3.—Lowest lesion is positive patch test with thurowort oil and almond oil. The more proximal lesions are sites of adhesive strips which were contaminated with thurowort oil. No reaction is seen at the sites of application of other weed oils.

eyelids. These symptoms would occur "when the weather got real hot." They were worse some years than others. There was no spreading of the trouble beyond the areas mentioned. The occurrence of symptoms seemed always to be associated with weed contacts.

The recent attack started about thirty days before he was seen by me. It began with the usual symptoms, but they progressed beyond the state previously experienced. The whole face and neck were involved. The skin of the face both appeared and felt generally coarse and hard or tense. The skin was thickened, red, hot, and weeping. Over the face and forehead were blotchy, slightly raised, reddish areas that showed a distinct tendency to coalesce. There was no definite scaling. The lesions extended from the hairline to under the chin and laterally to the ears, which were not involved in the process. There was intolerable itching and burning. The outer one-third of the eyebrows was very thin. The eyes were red, swollen, and painful (Fig. 1).

Fig. 4.—Result of patch test with small amount of whole residue from ether extraction of flower.

The routine allergic study yielded no information whatever. Because the complaints were so definitely associated with weeds, the patient was asked to send in specimens of weeds with which he came into contact. These proved to be lamb's-quarters, spiny amaranth, bindweed, and thurowort (*Eupatorium altissimum*) (Fig. 2). These were dried, and the whole plant was extracted with ether. After evaporation a small amount of the residue was rubbed up with almond oil, and patch tests were applied. A definitely positive reaction was seen to the material extracted from *Eupatorium altissimum* (Fig. 3). Ether extracts were made of the flowering parts and the leaf of the plant; there were positive patch tests reactions only to the flowering portion. A patch test of the crude undiluted residue was applied, and the patient was instructed to remove it when the slightest itching was noted. He did not do this, and the result of this test is seen in Fig. 4. The patch test was forty-eight hours old. A small amount of the unextracted flower material was

moistened and put on the unabraded skin, and a positive test was obtained (Fig. 5). The flowering part of the plant was suspected because of its light hairy character and because of the fact that the patient's wife said she was sure that he had been more uncomfortable after driving on the leeward side of a field in which there was a heavy growth of the offending plant.

The black tarry residue from the ether extraction was prepared by mixing with Coca's solution and glycerin without refining it as suggested by Brown, Milford, and Coca.[2] In order to get a satisfactory mixture, the materials were rubbed together with a spatula until the residue was taken up in the mixture. The mixture represented approximately a 10 per cent dilution. This was filtered to sterility and yielded a clear amber fluid which was diluted 1:10, and 0.05 c.c. were given subcutaneously with no untoward results. The dose was increased rather rapidly. The last dose was 0.60 c.c. of a 1:5 dilution.

Fig. 5.—Result of patch test with the flowering portion of thurowort.

After the second injection there was marked relief of the symptoms as well as the condition of the face. This improvement was rapidly progressive. At the end of the second week he was completely relieved of his symptoms. Treatment was continued two weeks longer.

The patient has not been seen since, but in a follow-up letter dated July, 1939, he states that he has never had a return of the malady. He is extremely careful, however, to avoid the offending plant.

The *Eupatorium altissimum* is a very common plant throughout the Middle West. It is commonly known as tall thurowort or boneset. The habitat is dry open spaces, and the blooming season is during September and October.

The symptoms in this case began the latter part of August, but at that time the weed had not only bloomed, but had developed the fine, dry, hairy flowers which are easily wind-borne for short distances. The growth of this plant varies from year to year. This year, 1939, very little has been seen in this locality, but the growth was rank during the summer and fall of 1935.

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Annual Review

ALLERGY IN DERMATOLOGY

A Critical Review of Recent Contributions

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CONTACT DERMATITIS

OF CONSIDERABLE importance in the literature of the past year is the monograph of Bonnevie[1] dealing with the etiology and pathogenesis of eczema. Especial attention is devoted to a consideration of the problems of allergic contact-type dermatitis. The many detailed case reports, as well as the work as a whole, merit careful study by everyone interested in eczematous skin diseases.

Despite the recent advances in our knowledge of the allergic mechanism underlying many cases of eczema, there is still a group of eczematous eruptions which are not well understood. Important among these diseases are the hand eczemas which are common in almost every dermatologic practice. One is often at a loss whether or not one should employ the patch test method in studying patients presenting these syndromes. The frequency with which housewives, surgeons, laundresses, dishwashers, and domestic servants present these hand eczemas makes one suspect that occupational contact with soap or other substances is an etiological or an important contributory factor. Nonetheless, patch tests with soaps or soap solutions have been unsatisfactory. Allergic hypersensitivity to soap or a constituent of soap has rarely been demonstrated, despite the fact that for many years there has been a general clinical impression that the use of soap is of etiological importance.

The past ten years have shown many advances in our knowledge (still incomplete) of the physiology of the skin in relation to acids and alkalis (Marchionini, Burckhardt, and others). Important among the contributions of the past year are the papers of Blank[2] and of Pillsbury and Shaffer.[3]

Blank has described a technique for the accurate measurement of the pH of the skin surface with the glass electrode and has furnished measurements for certain skin areas of children and adults with normal skin. Pillsbury and Shaffer[3] measured the pH of the skin surface by means of indicators. In general, the results of these independent investigations are in agreement. The latter authors demonstrated quite

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clearly that the normal skin can withstand a fairly strong acid solution (3N HCl, pH 2.0). On the other hand, alkali of pH 12.6 (from a comparative standpoint, considerably weaker as alkali than 3N HCl is as acid) usually produced a reaction. (Solutions were in contact with the skin for about twenty-four hours).

Along the same lines as the work discussed above, Blank[4] has studied the reaction of the skin to patch tests with various fatty acids. The test persons included a group with normal skin, a group with a clinical history of soap-irritability, and a group of patients with atopic dermatitis or contact-type dermatitis. In normal persons, the saturated fatty acids of low molecular weight produced a much greater number of reactions than did those of high molecular weight. In the groups with skin disease, this difference was still present, although the total number of reactions was much greater.

Further study of the reaction of the skin to fatty acids on skin sites moistened repeatedly with buffer solutions of varying pH indicated that "the amount of alkali which must be added before a fatty acid becomes an irritant increases with the increasing molecular weight of the acid."

These experiments indicate that the harmful effects of soap are probably governed by the combination of at least two factors which may be synergistic: the effect of the fatty acid on the skin, and the reaction of the skin to alkali. There is as yet, however, no universal agreement on this subject. Previous studies, such as those of Jordan, Walker, and Osborne,[5] and of Goldman,[5] have indicated that allergic hypersensitivity may sometimes play a part. True allergic hypersensitivity to soaps apparently is comparatively infrequent. Certainly, patch tests with undiluted soaps are not to be recommended in investigating eczematous eruptions in which soap is thought to play a part. A suspension of from 1 to 5 per cent soap in water is usually a suitable dilution for patch testing.

Studies of the experimental sensitization of man and animals have continued during the past year. Landsteiner and Chase[6] have studied further the problem raised by Strauss and Coca.[7] It will be recalled that the latter authors demonstrated that, if a monkey was sensitized to poison ivy by application of the extract to the skin of an arm, the sensitivity became general. If, however, a cuff the full thickness of the skin were first turned down on the arm, the hypersensitivity did not spread past the gap in the continuity of the skin. By applying poison ivy extract to an island of skin on the guinea pig, Landsteiner and Chase demonstrated that the hypersensitivity failed to become general only if the incision was deep enough to sever the lymphatics *beneath* the skin. Incision through the skin alone was not sufficient to prevent the spread. The authors conclude that free lymph circulation beneath the skin is necessary for the spread of the sensitization.

Haxthausen[8] has been unable to obtain similar results in human beings, using dinitrochlorbenzene as the sensitizing agent. The incisions in human beings were made deep into the corium, *but not through the skin to the underlying muscle*, as in the guinea pigs of Landsteiner and Chase. An interesting finding reported by Haxthausen is that freezing the skin with carbon dioxide snow at the site of the application of the sensitizing agent, from one to eight days after the sensitizing application, inhibited sensitization in about 80 per cent of the instances in which it was tried. This inhibition seems to affirm the importance of the epithelium in contact-type hypersensitivity. Ginsberg, Stewart, and Becker[9] studied the gross and microscopic appearances of the reactions to ragweed and dinitrochlorbenzene in guinea pigs sensitive to these substances. A small percentage of guinea pigs painted with an ether ragweed extract became hypersensitive to that extract. Continued daily painting resulted in desensitization in about one-half of them. A study of the histology of the skin reaction in the guinea pig showed certain resemblances to the reaction to poison ivy in human beings, but also marked differences. Intercellular edema of the epidermis was slight in guinea pigs and intense in man. Vesicles did not appear in the guinea pig reaction but were numerous in the human reaction. Round cell infiltration and edema of the cutis are diffuse in the guinea pig; the edema tends to be localized in the human being and the round cell infiltration tends to be perivascular.

These findings have been confirmed in unpublished experiments with dinitrochlorbenzene by Dr. Louis Dienes and one of the reviewers (J. G.). In part, on the basis of these findings, the reviewers believe that it cannot yet be concluded that the reaction elicited in animals by the application of allergens such as those mentioned above is necessarily in all respects comparable to allergic contact-type dermatitis in man.

The existence of unknown factors in the pathogenesis of contact-type dermatitis is emphasized by experiments of Sulzberger and Rostenberg, Jr.[10] Eighty-two persons were exposed to both dinitrochlorbenzene and p-nitrosodimethylanilin in a uniform fashion. Three weeks later tests revealed that 50 per cent were hypersensitive to the first-mentioned substance, 36 per cent to the other. Twenty persons were hypersensitive mainly to p-nitrosodimethylanilin, and nine, mainly to dinitrochlorbenzene. In twenty-one instances there was approximately equal sensitivity to each substance. In thirty-two instances no hypersensitivity developed to either substance.

No explanation for these differences in the development of sensitivity from person to person is available. It seems likely that there are many factors, both local and general, varying from individual to individual, which influence the process of sensitization. Our knowledge of the nature of these factors is meager in the extreme.

The variability of the process of sensitization has also been pointed out by Simon and Lotspeich.[11] Sensitivity did not develop in all persons on whose skin a concentrated poison ivy extract was applied. Some were entirely resistant. Of further interest is the finding that patch tests with serial dilutions of poison ivy extract, done before and after a series of intramuscular injections of concentrated extract, revealed no appreciable alteration of the degree of hypersensitivity. The authors found, in addition, that three commonly used treatments for acute contact dermatitis caused by poison ivy (calamine lotion, 5 per cent potassium permanganate solution, and 5 per cent lead acetate solution) appeared to be without influence upon the clinical course of the disease.

Zisserman and Birch[11a] have contributed a new study on the possible effectiveness of poison ivy injections in both the prophylaxis and treatment of poison ivy dermatitis. Nothing could more strongly emphasize the present uncertain status concerning the usefulness of specific measures in the prophylaxis of plant dermatitis. The authors first briefly review some of the previous studies. Without analyzing the variability of the extracts and methods used, or the variables of type and amount of clinical exposure, season of the year, age of patients, previous susceptibility, incidence of previous attacks, etc., the results as presented in the brief historical review were approximately as follows:

The following are among the authors who have reported favorable results from administration of extracts in the *specific treatment* of ivy dermatitis: Strickler, Williams and MacGregor, Bivings, Clock, Gowen, Sharlit, and Caulfeild.

The following are among those who have reported *no* beneficial effects of extracts used in *specific treatment:* Krause and Weidman, Corson, and Sompeyrac.

Among others, the following have reported the specific extracts to be effective in *prophylaxis* of poison ivy dermatitis: Clock, Gowan, Blank and Coca, Biederman, Caulfeild, and Molitch and Poliakoff (two reports).

On the other hand, there are some authors who report that specific injections are of *no prophylactic value*. These include Bachman and, now, Zisserman and Birch, with a controlled study on a group of 1,731 boys. Moreover, the unpublished study of Greenberg and Mallozzi, performed at the clinic of one of the reviewers several years ago, included a group of workers at a Civilian Conservation Corps camp. In these also no striking or general prophylactic effect could be demonstrated following the specific injections. The incidence of ivy dermatitis in the injected group (seventy-seven men) was only very slightly less than in a control group (forty-two men) under approximately identical conditions of subsequent clinical exposure.

These wide divergences in results require explanation and study, for the problem is of theoretic and practical importance far transcending

the immediate subject of poison ivy dermatitis. The question involved is simply: Can the allergic sensitivity in contact-type eczematous dermatitis be materially reduced or abolished by specific measures; and do or do not the results in ivy dermatitis indicate that physicians will some day be able, through specific measures, to prevent or materially reduce the incidence of allergic contact-type dermatitis in general, including the literally hundreds of thousands of cases due to the many thousands of different occupational and extraoccupational eczematogenous allergens?

The following are among the questions now awaiting solution: Are the divergent results due to the use of different extracts? Or to different dosage? Or to different routes of administration? Or to differences in degree of the subsequent exposures to the excitant on the part of the treated individual? Or to any other known factors? Or to mistakes and technical errors? Or to certain variables which are as yet entirely beyond our knowledge?

Allergic contact-type dermatitis is probably the most common of all allergic diseases of man. It seems, therefore, that no subject in allergy and dermatology is of greater significance or more urgently in need of further careful study.

Shelmire[12] has reported instances of contact-type dermatitis produced by weeds and has described a method for preparing extracts of weeds for patch testing. In over 10,000 control tests with these extracts, only four mildly positive reactions were found.

In the light of Shelmire's work, it seems almost certain that dermatologists must from time to time see and fail to recognize contact-type dermatitis caused by weeds. Extracts of weeds, prepared by Shelmire's method, should be available for clinical use. When these extracts are available, the incidence of such contact dermatitis may well be found to be high, especially in rural areas.

The increasing use of rotenone (the active ingredient of derris and cube) in insect and plant sprays indicates that it too may become (or may already be) an important cause of contact dermatitis. In this connection it is of interest that Racouchot[13] has described an eruption occurring in all workers coming in contact with powdered cube roots in a factory in which a rotenone insect spray was being manufactured. The eruption was limited to the region of the genitals. Unfortunately, no mention is made of patch tests, and the question of allergy is not discussed. The circumstances of this industrial dermatitis are such that one must suspect that it is allergic until the contrary is demonstrated.

A general consideration of industrial dermatoses (the most important of which is contact-type dermatitis) has been published by Strandberg and associates.[14] Especially recommended in this group of papers are Bonnevie's discussion of the etiology and pathogenesis of contact dermatitis and Boström's discussion of the patch test.

Bering[15] has suggested a classification of industrial dermatitis, dividing these skin diseases into three groups: 1. Dermatitis, which includes eruptions which result from local irritant (toxic) action. These eruptions do not tend to spread. 2. Dermatoses which depend upon the exhaustion of the defense mechanisms of the skin (Abnutzung). An example of a dermatosis belonging to this group is cement eczema. 3. Allergic contact-type dermatitis.

It appears questionable whether these three mechanisms are at the basis of all the various forms of eczematous reactions. And it seems almost impossible to follow Bering's proposal to limit the use of the word eczema to allergic contact-type dermatitis. However, we are in sympathy with attempts to clarify the problems of industrial dermatitis by better classification, based as far as possible upon pathogenesis. It seems to us that some confusion has resulted in the past and still results from the use of the term "contact dermatitis." This expression most often refers to allergic contact-type dermatitis, even though the word "allergic" is omitted. However, there are many instances of nonallergic dermatitis produced by contact with chemicals and other substances. These eruptions must not be confused with the allergic eruptions. Until some better classification is in general use, care must be taken to qualify the term "contact-type dermatitis," so that there shall be no confusion between allergic and nonallergic eruptions.

Mention must be made here of the review by Flandin and his collaborators[16, 17] of 1,000 cases of industrial dermatitis. While no new viewpoints are presented, nonetheless, the statistical study of these cases merits the attention of all physicians who have a special interest in industrial dermatitis.

An interesting and new industrial contact-type dermatitis has been reported by Watrous.[18] Four persons working for the first time with nicotinic acid, developed within an hour or so an erythematous maculopapular eruption, with itching and burning. Other workers failed to develop the eruption under similar conditions. While the author states that the pathogenesis of this eruption is unexplained, it seems probable that it is not the *usual allergic* contact-type dermatitis. The short time between exposure and eruption makes one suspect that the reaction was urticarial in nature, that the symptoms might have been produced by *transepidermal penetration* of the nicotinic acid. However, until further studies are done, this explanation remains pure hypothesis.

Zündel and Jentsch,[19] studying the occupational eczema of bakers, found that allergic hypersensitivity to cereals and to persulfate forms the basis for practically all the cases of this dermatosis. Hypersensitivity to persulfate (by patch test) was found to underlie the acute eczematous eruptions, while hypersensitivity to cereals (by intracutaneous test) was found in association with the infiltrated and lichenified

eruptions. These two allergic hypersensitivities were found to be independent of one another.

Rabeau and Ukrainczyk[20] have discussed the dermatitis of laundresses, pointing out that the Javelle water commonly used by these persons in France is a solution of sodium hypochlorite with potassium bichromate added as a stabilizer. These investigators found in their patients evidence of a double sensitivity to chlorine as well as to chromate.

In the reviewers' experience, hypersensitivity to chromate is common, but contact hypersensitivity to chlorine as such is extremely rare, if it exists at all. (While the role of chlorine-containing compounds in producing acneform eruptions may be allergic in nature, it certainly is not contact-type dermatitis of the same variety as chromate dermatitis.) We are not prepared to accept the conclusions of these authors in regard to chlorine until this question has been studied further, in particular with reference to the influence of the alkali present in Javelle water.

The *prevention* of industrial dermatitis, including allergic contact-type dermatitis, has received particular attention in the past few years. An excellent summary of recent advances in this field will be found in the paper by Klauder, Gross, and Brown.[21]

The new federal regulations covering foods, drugs, and cosmetics have been reviewed recently by Klumpp.[22] The requirements for labeling will now make it possible for the physician to determine much more easily than formerly which ingredient of a proprietary remedy may have caused the contact-type dermatitis which his patient presents. Paraphenylenediamine and the para red dyes (Color Index No. 44) have been eliminated from cosmetics. It is unfortunate that the limitations of our knowledge of the allergic reactions to organic dyes preclude a more thorough consideration of the allergic problems associated with the use of cosmetics. Nonetheless, the new regulations are a great step forward. One must admit that if every substance which could possibly sensitize were eliminated from cosmetics, very little, if anything, would be left!

Among the drugs indispensable to physicians and also among those which sensitize fairly frequently are the local anesthetics. Hollander[23] recently reported an instance of allergic contact-type dermatitis from pontocaine. In an interesting study, M. H. Goodman[24] reports that his patient with contact-type dermatitis produced by procaine showed positive patch tests to all para-aminobenzoate anesthetics; in fact, there were positive tests to anilin and to salts of para-aminobenzoic acid. On the other hand, there were negative patch tests to benzol, to salts of ortho- and meta-aminobenzoic acids, to alypin (benzoic acid derivative), and to local anesthetics of the quinolin and cocaine groups.

In this case there was a definite correlation of chemical structure and hypersensitivity. Observations of the reviewers during the past few years indicate that, in many instances of hypersensitivity to local anes-

thetics, this correlation either is not present or is considerably more obscure than in the patient studied by M. H. Goodman. Further studies of this sort will be of considerable interest.

Jordon's[25] report of contact-type dermatitis from opium derivatives, as well as that of Lamb[26] concerning quinine dermatitis following the ingestion of anacin, are of interest. The latter report serves as a reminder that allergic contact-type dermatitis may develop as a result of the ingestion or injection of a drug. The allergen in such cases is distributed hematogenously and reaches the shock tissue (epidermis) from within rather than from without. In these instances, patch tests with the drug are positive (contrary to the usual drug eruption, in which, as a general rule, all skin tests are negative). Outstanding among the causes in our cases of contact-type dermatitis from within are quinine, chloral hydrate, and mercury. (The fact that this form of dermatitis can be elicited also from within has impelled us to use the term "contact-type dermatitis" rather than "contact dermatitis.")

The report of Levison and Harrison[27] of dermatitis following injections of theelin is interesting and unusual. The reviewers believe, however, that the investigation of this case did not prove conclusively that the hormone was the cause of the eruption.

The report of Madden[28] on reactions in tattoos includes one case in which the red (cinnabar) portion of a tattoo was swollen and slightly itchy. This patient showed positive patch tests to mercury compounds. Previous authors, including Ballin, and the reviewers have observed similar cases, in which mercury hypersensitivity apparently developed several years after the tattoo had been completed. In these instances, too, the red portions became swollen and in some instances developed ulcers. (This rare eventuality may be of some significance in relation to Hollander's recently developed method of cinnabar tattooing in the treatment of pruritus ani or vulvae.)

The report of Bernstein[29] of dermatitis caused by a sulfur-meat complex is another instance of an eruption produced by sensitivity to a combination of two substances, neither of which alone is capable of eliciting the reaction. (Compare cable-splicers' dermatitis reported by Schwartz and Hocker and discussed in the 1937 review.)

Among the miscellaneous papers dealing with allergic contact-type dermatitis which remain for consideration, mention must be made of Bechet's[30] warning regarding the generalized eruptions which may sometimes result from patch tests, particularly when applied in a faulty fashion. Another danger, that of patch testing with an improper concentration of a substance, has been reduced, at least for the substances commonly used in testing, by the publication of the list of Rostenberg and Sulzberger.[31] For over 700 substances this list gives the concentration and vehicle to be used in performing the patch test. It is hoped

that this list can be revised, corrected, and supplemented from time to time, so that eventually very complete and accurate data will be available for a great number of substances.

Guild[32] has described a new method of patch testing which may be useful for investigative purposes.

Boström[33] has been unable to repeat his experiments concerning the metabolism reaction, discussed in the 1937 review of this series.

In concluding this section of the review, mention must be made of the symposium on allergic dermatoses which appeared in the JOURNAL OF ALLERGY in the past year.[34] Since this discussion is already familiar to readers of this journal, no further review is necessary here.

ATOPIC DERMATITIS

Tachau has discussed problems of infantile eczema in a series of papers which attempt to distinguish between the several varieties of this puzzling syndrome. In the first paper[35] he discusses "true eczema," under which heading he includes contact-type dermatitis, the common "milk crust," intertriginous lesions (including "ammonia dermatitis"), and scalp eczema caused by external irritants.

In the experience of the reviewers, external irritation often plays a part in such eruptions, but it is doubtful that the mechanism is usually that which is responsible for allergic contact-type dermatitis. An atopic background seems frequent in patients with such eruptions. It seems probable that the atopic infant, as a result of his constitutional and familial tendencies, is equipped with a skin which has a decreased ability to withstand many forms of nonspecific irritation (ammonia, soap, cold, light, microorganisms, etc.) or certain other forms of allergic sensitization.

In the second paper of the series,[36] Tachau discusses atopic dermatitis in the infant. The reviewers are firmly in agreement with Tachau's rejection of the word eczema here in favor of "atopic dermatitis." We do not agree, however, that the lichen chronicus circumscriptus is commonly found in children or that, in children or adults, it is related to atopic dermatitis.

In the third paper of the series,[37] Tachau discusses diseases of the seborrheic group in infants. While such diseases do occur in infants and children, they are, in our experience, quite rare. They are, in the light of present knowledge, not considered allergic diseases. In general, the reviewers find great difficulty in distinguishing these infantile eczema syndromes one from another on the basis of their morphology. For the present, therefore, we prefer to speak of eczema in the infant without attempting to divide the group, but nonetheless recognizing the importance of allergic (atopic) mechanisms and nonallergic contact factors. As far as adults, and perhaps older children as well, are concerned, division into groups, as suggested by Tachau, seems entirely feasible.

Lippard[38] studied the immunologic responses of normal and eczematous infants to egg white and to milk. Forty normal infants who had never eaten egg showed no skin reaction (urticarial) to egg white. Twenty infants who had been fed cooked egg showed only one positive complement fixation to egg white. After the administration of raw egg white, however, five of nine cases showed a positive intracutaneous test and complement fixation. On the other hand, ten of twenty-one infants with eczema showed a positive urticarial reaction to egg white, although they had never been fed egg. Of sixteen eczematous babies who had been fed small amounts of egg, fifteen showed a positive skin test. Both the normal and the eczema group showed reactions (at least complement fixation) to milk. These reactions were transitory in the normal infants.

The findings presented in this study are, on the whole, confirmatory of the so-called "Schloss phenomenon."[39] Normal infants go through a phase of sensitivity to new allergens. Unlike the atopic person the normal individual has few manifestations of this allergic hypersensitivity which is soon lost (immunization?). The atopic person, on the other hand, becomes sensitive and stays sensitive for an abnormal length of time. He fails to become immunized to the new exposures at the normal rate or in the normal manner. But the evidence presented by Lippard would indicate that the atopic baby, in addition, *becomes* sensitive more easily. This may be true for infants but, as Simon and Rackemann[40] have demonstrated, it is not true for adults, at least as regards certain selected allergens.

Clein[41] has studied the first allergic manifestations in infants. Eighty-two of 100 allergic infants developed a rash on the face as the first allergic manifestation. It is of interest that twenty-one of this group of 100 developed allergic symptoms while still on the breast. All but three of these cases cleared up when certain foods were eliminated from the mother's diet.

Feinberg[42] has discussed the role of inhalant allergens, particularly pollens, in seasonal atopic dermatitis. His conclusions agree with those generally accepted that pollens are important factors in this disease. In the reviewers' experience, it is extremely rarely that pollens are apparently the only or the one major factor in atopic dermatitis, even in cases with very apparent seasonal exacerbations. Unfortunately for the allergic approach, in adult or adolescent persons with atopic dermatitis, the etiological factors are often exceedingly numerous.

Laymon and Cumming[43] have reported that atopic dermatitis was influenced relatively little by histaminase given over a period of from one to two months. In eight cases which these authors studied there was no improvement which could be attributed to the use of histaminase. This finding is disappointing, for a reliable means of relieving the

itching of patients with this disease would be more than welcome. The use of the appropriate topical remedy plus roentgen rays is still the best therapeutic approach.

These negative experiences with histaminase (torantil) coincide with those of the reviewers. The drug has proved itself of little or no value in our hands. (See also the discussion of urticaria.)

URTICARIA AND URTICARIAL REACTIONS TO SKIN TESTS

The problem of the management of chronic urticaria remains a difficult one. Certain authors report favorably on the use of histaminase.[43] Of seventeen patients with urticaria of several weeks' duration, ten (60 per cent) were cured clinically by the use of histaminase, orally and by injection. Two patients were improved, and five were unimproved.

However, the number of cases reported is still too small. The course of urticaria is too capricious to permit the drawing of conclusions, except from studies of large numbers of patients with long-standing urticaria. In Europe, histaminase in the form of "torantil" has been available for both injection and oral administration. It has been used for many years in the attempted treatment of all the various manifestations of allergy. Almost all the investigators now agree that the drug has proved generally disappointing, although its effect may have seemed beneficial in isolated instances. Allergists and dermatologists in this country will watch the results of the next few years' work with histaminase with considerable interest. Our own experience with histaminase (torantil) in all forms of allergy, as well as in urticarias due to cold or other factors, has thus far failed to demonstrate any therapeutic effect.

Traut[44] has reported success in the management of chronic urticaria by means of autogenous (stool) streptococcal vaccines. This method of treatment has been reported to be useful in the past. As this investigation indicates, it certainly should be given a trial in long-standing resistant cases. In general, the reviewers have had only indifferent success with autogenous vaccines.

Markel[45] has reported the case of a patient with chronic urticaria and angioneurotic edema, in whom there were signs of pancreatic insufficiency. The administration of deinsulinized pancreatic extract resulted in a cure. Although such cases must be rare, a report of this sort is particularly useful as a reminder of the many and varied etiological factors which must be considered during the investigation of urticaria. As an example, Urbach and his collaborators[46] have reported an instance of urticaria brought on by the ingestion of pork blood in the form of sausage. Pork meat and the other constituents of the sausage had no effect.

Harkavy[47] has studied urticarial reactions to skin tests with tobacco extract in thromboangiitis obliterans. In general, such skin tests are

specific, and sometimes they are significant. Edwards and his collaborators[48] have described a skin test which may be useful in following the serum therapy of pneumonia.

Important contributions are those of Harry Eagle and his collaborators, and of Sherman, Stull, and Hampton.[49] These investigators demonstrated that the serum of guinea pigs sensitized by injection of alum-precipitated pollen toxoid contained a substance which would produce passive sensitization of human skin. This power to sensitize passively was transitory.

Kahn[50] has reported what is apparently a most unusual occurrence—an acneform eruption from the nasal application of pollen in a hay fever patient. Shortly after the application, there was itching, burning, redness, and swelling of one cheek. Later acneform lesions appeared.

The dermatologist not infrequently sees acneform eruptions associated with itching. In rare instances the acne lesions start as wheals. The case reported by Kahn should encourage the attempt to discover a specific allergen when itching is a prominent feature of an acneform dermatosis. In some such cases foods and other allergens may act as "trigger factors"; and such excitants can even produce exacerbations of acne vulgaris. It is, however, to be recalled that in all these cases there is no evidence of atopy, and skin tests are generally useless in attempting to discover the clinically culpable allergens.

DRUG ERUPTIONS

The "erythema of the ninth day" of Milian is a type of arsphenamine reaction which merits the attention recently given it by Cañizares and Thomas.[51] In a study of eleven cases of this eruption, the authors found that, in most instances, arsenical drugs could be administered without reaction after the disappearance of the eruption. Three patients were given further arsphenamine without reaction even before the eruption had disappeared. In two of the eleven cases, further arsphenamine was not tolerated. In general, the best procedure is to interrupt treatment until the skin is clear and then to resume it cautiously. The mechanism of such eruptions remains obscure. The explanation proposed by Milian (the activation of a virus such as that of measles) merits further study but is by no means generally accepted as yet.

Golz[52] has reported an instance of hypersensitivity to both trivalent and pentavalent arsenical drugs. Several months after developing an exfoliative dermatitis from neoarsphenamine, the patient was given one injection of tryparsamide. Within four hours after the injection, the first signs of a recurrence of the exfoliative dermatitis appeared.

A sensitivity such as this one is rare. This report serves to emphasize the fact that there is considerable variation from patient to patient in arsphenamine dermatitis. Sometimes the sensitivity is directed toward

one of the group of trivalent arsenicals, at other times toward all trivalent compounds, and in rare instances, toward all arsenicals irrespective of valence. Unfortunately, patch tests cannot be relied upon in arsenical exfoliative dermatitis. The patient reported by Golz had positive patch tests to all the arsenicals tested. Tryparsamide, however, showed the weakest reaction.

The investigation by animal experiment of the comparative sensitizing properties of various arsenicals, as first carried out by Frank A. Simon and one of the reviewers, is assuming more importance. Schnitzer[53] and Miescher and Schnitzer[54] have recently published experiments which tend to show that arsenoxide (mapharsen) sensitizes animals less frequently than do other arsenicals.

It is hoped that the major danger of exfoliative dermatitis from arsphenamine may be avoided by the use of the intravenous drip method of treating syphilis.[55] With this procedure, treatment is concluded before the completion of the usual incubation period for the development of the type of sensitivity which leads to exfoliative dermatitis. Unfortunately, relatively minor reactions are not infrequent, and there has been one death in the series reported. With further study, however, it is possible that the rapid administration of a massive dose of an arsenical, particularly of a weakly allergenic arsenical such as mapharsen, may prove to be the treatment of choice for early syphilis. It is difficult to justify the use of this form of treatment in latent or late syphilis.

Among drug eruptions, those which follow the use of sulfanilamide, sulfapyridine, etc., have assumed considerable importance. Many reports are present in the recent literature. Since particular attention was paid to this subject in last year's review, it will suffice to mention Garvin's[56] excellent summary of skin reactions and other manifestations of intolerance to this group of drugs. Among the skin manifestations there have been reported exfoliative dermatitis, morbilliform, scarlatiniform, and varioliform eruptions, urticaria and angioneurotic edema, purpura, and photosensitivity.

It has been reported again that purpura follows the use of sedormid, McGovern and Wright[57] having observed it twice in one person.

Golden and Gierson[58] report that guinea pigs can be sensitized to amidopyrine to the extent of showing a skin reaction. Unfortunately, this work, as well as other animal experimentation with similar drugs, has been, on the whole, far from conclusive and has done little to further our knowledge of the pathogenesis of drug eruptions. With the exception of those eruptions which can be classed pathogenetically with contact dermatitis, and with the exception of arsphenamine sensitizations, we have little knowledge of the precise mechanism of drug eruptions in

animals. The evidence indicates, however, that at least a large number of human drug eruptions are allergic. Further than that it is impossible to go at the present time.

SKIN ALLERGY IN INFECTIOUS DISEASES

Turner[59] has produced fairly convincing evidence of the presence of protective antibodies in the serum of rabbits infected with syphilis. These antibodies can be demonstrated about six months after infection. Mixtures of tissue emulsion from rabbit chancres and of serum from rabbits infected with an homologous strain of spirochetes are incubated at 37° C. and then inoculated into previously uninfected animals. A comparison of the lesion resulting from the inoculation of this mixture and the lesion resulting from the inoculation of a mixture of the same emulsion with normal rabbit serum demonstrated quite clearly that the serum from the infected animals contained spirocheticidal antibodies. This conclusion was reached because of the later appearance of the lesions which resulted from the inoculation of the immune mixture, the decreased size of the lesions, and in some instances, the complete absence of lesions.

This contribution is of importance as a direct demonstration of circulating antibodies in experimental syphilis. The controversy between Chesney and Kolle (referred to previously in these reviews) was concerned with the nature of the change in reactivity which appears after infection with syphilis. While these two investigators were in accord as far as experimental data were concerned, their interpretation of these data differed. Chesney maintained that there was a true immunity in syphilis; Kolle, that there was no true immunity, but only a state which he referred to as "chancre-immunity." If Turner's work is accepted, there can be no further disagreement on this point, for the demonstration of circulating antibodies is incontrovertible evidence of true, even though incomplete, immunity.

Becker[60] has confirmed observations previously made by Eagle[61] on the antigenicity of flocculate obtained from the serum of patients with syphilis. While this work is by no means as direct and fundamental an observation as that of Turner, nevertheless, it offers additional support to the proponents of true immunity in syphilis.

The Frei test has come to be generally accepted as a specific reaction. It is of interest that the intravenous injection of 0.1 c.c. of the mouse brain antigen (prepared from the brains of mice infected with lymphogranuloma inguinale) gives a typical febrile response in patients who have had lymphogranuloma inguinale. Decker, Cañizares, and Reider[62] found this test to be specific and useful as a confirmation of the skin test.

Franchi[63] has studied the histology of the positive Frei test in comparison to the histology of nodular reactions to other antigens (streptococcus, staphylococcus, etc.). Only in the positive Frei test was there

a tuberculoid structure. This study again emphasizes the fact that substances other than the tubercle bacillus or its lipoids can produce a tuberculoid type of reaction.

Keim and Wakefield[64] have reported an interesting case of flaccid paraplegia following a diagnostic intradermal injection of Frei antigen. Reactions of this sort have been reported to follow injections of other unrelated substances. It is not known definitely that such reactions are allergic. The incubation period (in this case, eleven days) gives support to those who believe that an allergic reaction is in the background.

Among the newer recent skin tests are those for echinococcal disease and for coccidioidal granuloma. Rose and Culbertson[65] have described a skin test which is believed to be specific for echinococcus infection. Kessel[66] has described a skin reaction of the tuberculin type (twenty-four to forty-eight hour) to coccidioidin. Of twenty-six patients with proved infection with *Coccidioides immitis*, twenty-two showed a positive tuberculin-type skin reaction. The four patients who had no reactions were in the advanced stages of the disease (possibly anergic). The results of extensive control tests indicate that this reaction is specific. Jacobson[67] has reported good results from the specific immunization with coccidioidin.

Anderson and Stokes[68] have studied the use of staphylococcus toxoid and ambotoxoid (toxoid plus vaccine) in furunculosis, acne vulgaris, and other resistant pyogenic dermatoses. Most interesting from the immunologic standpoint is the fact that, just as reported by Sulzberger and G. Rubin, the clinical result did not parallel the increase in staphylococcus antitoxin titer of the blood.

This finding is an example of a condition which obtains in various skin diseases. The factor of the immune state of the skin itself often appears to be of greater importance than the presence or absence of circulating antibodies. Haxthausen[69] has performed an ingenious experiment designed to demonstrate the independence of the skin in the production of sensitivity. Three groups of fifteen persons were injected with horse serum in three different ways. Group I received 0.1 c.c. intravenously; Group II received 0.1 c.c. intracutaneously on the left forearm; and Group III received ten subcutaneous injections of a 1:10 dilution of horse serum in various scattered sites. After fourteen days all subjects were tested by the injection of 0.1 c.c. each of three horse serum dilutions (10, 1, and 0.1 per cent) in the right upper arm. In Group I only three persons showed skin reactions to the test injections. The persons in Groups II and III showed more frequent and more intense sensitivity than those in Group I.

There is a large body of older experimental work which indicates that the skin has considerable independence in allergic states. The part

played by the skin in originating and in modifying allergy is often overlooked. Haxthausen's work emphasizes once more the importance of the allergic state of the skin as contrasted to the general allergic state of the individual.

TUBERCULIN AND TRICHOPHYTIN ALLERGY

Considerable interest has been manifested in the past few years in the patch test with tuberculin as a substitute for the Pirquet or Mantoux test. Vollmer and Goldberger[70] have carried out a comparative study of the Mantoux test and the patch test on 678 children, of whom 261 were known to have active tuberculosis. This study was, in general, confirmatory of these authors' previous investigation, which was discussed in last year's review. Their most recent work indicates that the patch test has 100 per cent reliability as compared to the intradermal test with the first strength of purified protein derivative and better than 99 per cent reliability when compared with second strength P.P.D. Court[71] and others have likewise found the tuberculin patch test reliable.

In our discussion last year it was pointed out that there was still much to learn about the tuberculin patch test. The same can be said at this writing. An investigation of the histologic characteristics of the reaction will be of considerable interest.

A series of papers which discuss various aspects of erythema nodosum[72] leaves one with a conclusion which has been expressed before in these reviews: that erythema nodosum is a symptom complex and not an independent disease entity. In the papers cited above, there is some difference of opinion in regard to the cause of this eruption. A few, such as Rabeau and Ukrainczyk, find it to be of tuberculous origin. The undeniable fact that erythema nodosum may be part of rheumatic infection, tularemia, gonococcus infection, lymphogranuloma inguinale, infection with *Coccidioides immitis*, etc., or that it may be a drug eruption makes it impossible for the reviewers to consider it a tuberculous disease. In some clinical groups tuberculosis is undoubtedly a common cause of erythema nodosum; but it is by no means the only cause of this eruption.

Allergic aspects of fungous infections have received comparatively little attention during the past year. However, among the many case reports which have appeared in the literature is one which merits particular attention. Wiesmann[73] investigated a patient with a lichenoid trichophytid. In the skin as well as in the enlarged regional lymph nodes, mycelial threads could be demonstrated. Cultures of material taken from the glands were negative. The author believes that the cultures were negative because the organisms were either weakened or killed by the allergic reaction which they aroused.

In general, the demonstration of fungi in the lesion of the epidermophytid eruption or in lymph nodes or blood of patients who present such

eruptions is difficult. It has been accomplished only rarely. Yet the whole theory of the "id" rests mainly on the foundation of those cases in which such demonstrations have been possible. The addition of even one more case to those already recorded is welcome.

Just as was the case in previous years, in this review also there have been many omissions and oversights, for which the authors wish to apologize in advance. During the past year the main interest has been in contact-type dermatitis in general, and in the use of histamine and histaminase in urticaria and atopic diseases. Since investigative work in Europe will be largely impossible during 1940, it is hoped that there will be increased contributions to the next year's literature from North and South America. The problems which remain for study are many. Their importance is such that they should attract our ablest investigators.

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Society Proceedings

Hospitals With Allergy Clinics Approved by the Joint Committee on Standards for the American Society for the Study of Allergy and the Society for the Study of Asthma and Allied Conditions, up to February, 1940.

ARIZONA

Phoenix

1. St. Luke's Home

CALIFORNIA

Los Angeles

2. Children's Hospital
3. Los Angeles County General Hospital
4. Santa Fe Coast Lines Hospital

DISTRICT OF COLUMBIA

Washington

5. Children's Hospital

INDIANA

Indianapolis

6. James Whitcomb Riley Hospital for Children

MARYLAND

Baltimore

7. Johns Hopkins Hospital

MASSACHUSETTS

Boston

8. Beth Israel Hospital
9. Massachusetts General Hospital

MINNESOTA

Rochester

10. Mayo Clinic

MISSOURI

St. Louis

11. Barnes Hospital
12. Firmin Desloge Hospital
13. McMillan Hospital

NEW JERSEY

Montclair

14. Mountainside Hospital

NEW YORK

Brooklyn

15. Beth-El Hospital
16. Jewish Hospital

Buffalo

17. Buffalo General Hospital
18. Children's Hospital of Buffalo

New York

19. Bellevue Hospital, Third Division
20. Bellevue Hospital, Children's Division
21. Beth-Israel Hospital
22. French Hospital
23. Gouverneur Hospital
24. Lebanon Hospital
25. Midtown Hospital
26. Mount Sinai Hospital
27. New York Hospital
28. New York Eye and Ear Hospital
29. New York Infirmary for Women and Children
30. New York Polyclinic Medical School and Hospital
31. New York Post-Graduate Hospital, Department of Medicine
32. New York Post-Graduate Hospital, Department of Pediatrics
33. New York Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital
34. New York University Medical Clinic
35. Roosevelt Hospital
36. St. Luke's Hospital
37. Sydenham Hospital

Rochester

38. Rochester General Hospital
39. Strong Memorial Hospital

Syracuse

40. Syracuse Free Dispensary

PENNSYLVANIA

Philadelphia

41. Children's Hospital
42. Germantown Hospital
43. Graduate Hospital of the University of Pennsylvania
44. Hospital of the University of Pennsylvania
45. Jefferson Hospital
46. Mount Sinai Hospital
47. Pennsylvania Hospital
48. Philadelphia General Hospital
49. Temple University Hospital

Pittsburgh

50. University of Pittsburgh Hospital, Falk Clinic
51. United States Veterans Administration Hospital

VIRGINIA

Richmond

52. Medical College of Virginia, Hospital Division

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., AND
THEODORE B. BERNSTEIN, M.D., CHICAGO

Immunological Studies of Pollinosis: I. The Presence of Two Antibodies Related to the Same Pollen-Antigen in the Serum of Treated Hay Fever Patients. Loveless, M. H.: J. Immunol. **38**: 25, 1940.

Loveless presents evidence showing that the antibody produced either in sensitive or in nonsensitive persons by the parenteral administration of ragweed extract (the so-called "inhibitory" or blocking antibody of Cooke) produces its effect by combining with the antigen which had produced it, and not by attaching itself to reagin. This antibody was also shown to exhibit thermostabile properties, for its capacity to bind antigen was not lost by heating to 56° C. for as long as five hours, or to 60° C. for from one-half to one hour. In this way it differs from reagin, which loses its skin-sensitizing properties under similar treatment. It was also confirmed that the antigen-binding, thermostabile, nonsensitizing antibody could be developed in both normal and sensitive persons after ragweed pollen injection. The thermostabile antibody was shown to disappear rapidly from an inoculated cutaneous site in less than twenty-four hours, whereas reagin remains at a locally injected site for weeks.

The Medical and Surgical Treatment of Severe Bronchial Asthma. Keeney, E. L.: Bull. Johns Hopkins Hosp. **66**: 34, 1940.

In discussing the treatment of patients with severe bronchial asthma, Keeney speaks of three groups. Group 1 consists of patients with severe acute asthma, Group 2 of patients with intractable asthma, and Group 3 of those with severe chronic asthma. The treatment of those in Group 1 consists of injection of from 0.3 to 0.5 c.c. epinephrine hydrochloride 1:1,000, repeated every fifteen minutes until four doses are administered or until relief is apparent. Epinephrine in oil is used to prevent a recurrence. The suggested treatment for patients in Group 2 consists of intravenous sucrose (100 c.c. of 50 per cent sucrose to which has been added 0.5 c.c. epinephrine 1:1,000), intravenous aminophyllin, inhalation of helium-oxygen mixtures, ether in oil administered rectally, and digitalization. For those in Group 3 epinephrine in oil is suggested, since fewer injections are required. The merits of certain surgical procedures are considered.

Relation of Histaminase to Intestinal Toxemia and Asthma: Preliminary Report. Eustis, A.: New Orleans M. & S. J. **92**: 349, 1940.

Eustis cites the histories of four patients whose asthmatic symptoms were controlled by ingestion of histaminase, in addition to a low histidine diet. He advocates large doses of histaminase at first in order to neutralize histamine occurring in the intestinal canal as the result of breaking up of the amino acid histidine. With a low histidine diet, only small amounts of histamine will be formed, and, consequently, only small doses of histaminase need be given later.

Pollen Disease in Western Canada. Walton, C. H. A.: Canad. M. A. J. 42: 62, 1940.

This report is a brief outline of progress made in a pollen survey of western Canada. The first pollen appears about April 24, and this tree season spreads over a period of from five to six weeks. The first pollinating trees are poplars and hazels, followed later by the willows and birches. Other tree pollens are those of the box elder, American elm, ash, and scrub oak. The box elder and elm produce large quantities of pollen. The grasses begin to pollinate in early June, and the worst of the season is over by the first week in July. The docks and sorrels are widespread, but their clinical significance is not clear; they pollinate from the middle of June to the last of July. Plantain is a factor of importance and pollinates through most of the summer.

The ragweed pollen counts are low, and the pollen is only one of several important factors in cases occurring in the fall. Russian thistle and sage are important hay fever producers in the fall. There are sixteen varieties of Russian thistle, which is widespread; sage, ten species of which have been found, occurs in heavy growths. The pollens of both of these plants are toxic, and although the sage pollen counts are low, both are important causes of fall pollinosis either by themselves or in association with ragweed pollen.

Dermatology

UNDER THE DIRECTION OF MARION SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

De la signification des bacilles tuberculeux démonstrables dans les nodules de l'érythème noueux. Wallgren, A., and Gnosspelius, A.: Acta med. Scandinav. 103: 341, 1940.

After pointing out the rarity with which acid-fast bacilli have been found in the nodules of erythema nodosum, the authors review their findings in eight cases. Four patients presented positive tuberculin tests, and four negative tests (repeatedly). A biopsy was done in each instance, and in none were acid-fast bacilli found, even in serial sections. After discussing the allergic aspects of erythema nodosum, the authors conclude that the reaction in the skin is specific and allergic, but by no means is it always related to tuberculous infection.

Untersuchungen über die Bienengift-empfindlichkeit der Haut bei allergischen Erkrankungen. Traub, E.: Acta paediat. 27: 177, 1939.

Studies of the skin reaction to bee venom (a parallergic irritant) were undertaken in patients with bronchial asthma, rheumatic fever, tuberculosis, bronchopneumonia, scarlet fever, and catarrhal jaundice. In bronchial asthma there was a great increase in the sensitivity of the skin to this substance. In patients with acute rheumatic polyarthritis there was considerable hypersensitivity to bee venom, less in patients showing a beginning or well-established cardiac lesion. In tuberculosis the reaction ran more or less parallel to the reaction to old tuberculin. On the contrary, in bronchopneumonia there was a lessened sensitivity, as there was also in scarlet fever. In catarrhal jaundice there was a definite hypersensitivity to bee venom.

An Attempt to Analyze the Tuberculin Anergy in Schaumann's Disease (Boeck's "Sarcoid") and Uveoparotid Fever by Means of B.C.G. Vaccination. Lemming, R.: Acta med. Scandinav. 103: 400, 1940.

The author has attempted to ascertain whether the tuberculin anergy, observed in cases of sarcoid and related diseases, is a specific (positive) anergy or whether it is merely the lack of reaction which one would expect to find in the person who had never come in contact with the tubercle bacillus. The inoculation of normal persons with B.C.G. vaccine regularly leads to the development of a positive tuberculin test. Lemming reasoned that, if the lack of reaction to tuberculin characteristic of patients with sarcoid were of the latter variety (no contact), the tuberculin test should become positive in the usual fashion after inoculation with B.C.G. vaccine. If, however, the lack of reaction were based upon a specific allergic alteration, there might be no positive tuberculin test, even though the amount of vaccine given were greater than usual.

This experiment was performed on two patients, one with uveoparotid fever and one with the more usual picture of sarcoid. In neither did a positive tuberculin test develop. This finding indicates that the tuberculin anergy of the sarcoid diseases is specific and allergic.

Studies on the Sensitization of Animals With Simple Chemical Compounds. VII. Skin Sensitization by Intraperitoneal Injections. Landsteiner, K., and Chase, M. W.: J. Exper. Med. 71: 237, 1940.

In general, experimental skin sensitization with simple chemicals has been produced only by application of the antigen on or into the skin. However, the author found that in the guinea pig the intraperitoneal injection of a suspension of killed tubercle bacilli in paraffin oil, followed on the second or third day by the intraperitoneal injection of from 0.2 to 0.5 mg. of picryl chloride dissolved in saline or dissolved in a paraffin oil-tubercle bacillus suspension, resulted fairly regularly in the production of skin-sensitivity to picryl chloride. On the other hand, control tests (picryl chloride in paraffin oil, without added tubercle bacilli) resulted only sporadically in definite skin-sensitivity. Other similar experiments with combinations of dinitrochlorbenzene with alumina and of poison ivy extract with tapioca gave results which were by no means as regular as those obtained with the picryl chloride-tubercle bacillus mixture.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND
MAX HARTEN, M.D., BROOKLYN

Some Observations on Reversed Anaphylaxis. Van den Ende, M.: J. Hygiene 39: 471, 1939.

The object of these experiments was to determine whether the shock syndrome evolved in reverse anaphylaxis in the guinea pig is due to the occurrence of a precipitating reaction in the blood of the test animal, or whether the antiserum reacts with antigenic constituents of the tissue cells.

The symptoms and autopsy findings of the acutely fatal cases of reversed anaphylaxis revealed striking similarities to those found in true anaphylactic shock in the guinea pig. They differed from direct anaphylaxis in that the lungs

were more pink and presented a large number of capillary hemorrhages. Delayed shock reactions displayed a great similarity to the usual form of anaphylaxis observed in the dog.

The alterations in systemic blood pressure, pulmonary arterial pressure, and bronchial resistance were found to simulate closely those observable in anaphylactic shock.

The potency of a serum to produce reverse anaphylactic shock in guinea pigs was found to depend primarily upon its precipitin content. The shock was the result of an antigen-antibody reaction occurring in the protoplasm of the tissue cells. Reversed anaphylaxis was observed to differ from direct anaphylaxis only in its independence of previous sensitization to a foreign protein.

Effect of Histaminase Treatment on Histamine and Anaphylactic Shock in Guinea Pigs. Karady, S., and Browne, J. S. L.: J. Immunol. **37**: 463, 1939.

Studies on the effect of histaminase administration upon anaphylactic and histamine shock in guinea pigs are reported.

The intravenous injection of three units (histamine-destroying units) of histaminase fifteen minutes prior to the intra-abdominal injection of 4 mg. of histamine dihydrochloride inhibited symptoms of histamine shock in the majority of guinea pigs so treated. Seven of ten control animals died with typical symptoms of histamine shock, whereas only six of the twenty treated animals presented shock symptoms, which were mild and delayed. Two of these, however, died in fatal histamine shock thirty-five minutes following the histamine injection.

A similar amount of histaminase injected intrajugularly fifteen minutes before the intra-abdominal injection of the shocking dose in guinea pigs previously sensitized to egg white inhibited anaphylactic shock in fifteen of twenty animals so treated. The five remaining animals presented very mild and delayed anaphylactic symptoms. All of the ten control animals exhibited severe anaphylactic symptoms.

The inhibiting action of histaminase on histamine and anaphylactic shock in the guinea pig justifies its therapeutic use in the clinical allergies in human beings.

Blood Histamine in the Rabbit During Anaphylactic Shock. Rose, B., and Weil, P.: Proc. Soc. Exper. Biol. & Med. **42**: 494, 1939.

During the course of investigations on anaphylactic shock in the rabbit, blood histamine determinations were made on the whole blood and on the plasma by the Code modification of the Barsoum and Gaddum method.

Rabbits were sensitized by the intraperitoneal administration of three successive doses of 2 c.c. of horse serum at four-day intervals. The shock dose consisted of 6 c.c. of horse serum given intravenously from three to four weeks after the last sensitizing dose. Blood specimens were removed by cardiac puncture prior to the administration of the shocking dose and again from four to fifteen minutes following its injection.

In all animals a marked decrease in total blood histamine during anaphylactic shock was observed. No consistent changes in plasma histamine were noted. There was no correlation between the severity of the anaphylactic symptoms and the degree of change in the histamine content of the blood.

The results obtained in these experiments differ from those reported by Code in which an increase of the total blood and plasma histamine was observed. They are, however, similar to changes in the total blood histamine during anaphylactic shock in the horse and calf, which were reported recently by Code and Hester.

On Cross Reactions of Egg Albumin Sera. Landsteiner, K., and van der Scheer, J.: J. Exper. Med. **71**: 445, 1940.

Exhaustion of a serum with a related heterologous protein may abolish the reaction of the serum to this antigen, and often also to other related antigens, without seriously impairing the ability of the serum to precipitate homologous antigen. In the present studies rabbits received one, two, and occasionally three courses of injections of hen ovalbumen at weekly intervals. Each course consisted of six daily injections of 2 c.c. of a 0.6 per cent solution of hen ovalbumen. The immune sera obtained were tested seven days after the last injection against the crystalline egg albumens of chicken, turkey, guinea hen, duck, and goose by means of precipitin, exhaustion, and inhibition tests.

All albumens gave precipitin reactions with anti-hen ovalbumen serum. The intensity of the precipitin reaction diminished in the following order: hen, turkey, guinea hen, duck, goose, pigeon. The results of exhaustion and inhibition tests indicated that the prepared sera contained multiple, qualitatively distinct antibodies.

Two explanations are offered. The first assumes the presence in protein of a number of different complex determinants. Previous experiments by the same authors indicated that one antigenic grouping can elicit formation of diverse antibodies. The second explanation infers that cross reactions between proteins of kindred species are ascribable, in general, to similarity in determinant structures and not to the distribution of identical determinant groups among related proteins.

The Synergistic Effect of Paraffin Oil Combined With Heat-Killed Tubercle Bacilli. Freund, J., Casals-Ariet, J., and Genghof, D. S.: J. Immunol. **38**: 67, 1940.

The literature on the synergistic effect of paraffin oil combined with heat-killed tubercle bacilli is reviewed. Because the injection of tubercle bacilli in paraffin oil is commonly followed by extensive, often suppurating lesions, the present studies were performed to determine an amount of paraffin oil which would be sufficient to exert a definite synergistic effect without inducing extensive suppurative local lesions.

Four groups of rabbits were given four simultaneous subcutaneous injections of 0.1 mg. heat-killed tubercle bacilli suspended in paraffin oil; a fifth group similarly received heat-killed tubercle bacilli in salt solution. Four series of such injections were administered at weekly intervals. The amounts of paraffin oil added to the antigen in the four groups of animals were 0.03 c.c., 0.002 c.c., 0.0005 c.c., and 0.0001 c.c., respectively. The size of the local lesions, skin-sensitivity to tuberculin, and antibody formation were recorded.

Specific sensitivity and antibody formation induced by paraffin oil and heat-killed tubercle bacilli injected subcutaneously into rabbits were found to be proportional to the amount of paraffin oil used and the size of the lesions produced. The authors demonstrate that it is possible to produce in rabbits intense sensitivity and considerable antibody formation in the absence of suppuration or necrosis of the skin. However, an amount of paraffin oil sufficient to enclose the tubercle bacilli, but insufficient to produce conspicuous lesions in combination with tubercle bacilli, has no demonstrable synergistic effect.

Antibody Formation in a Tuberculous Lesion at the Site of Inoculation. Westwater, J. O.: J. Exper. Med. **71**: 455, 1940.

The author attempted to determine whether the appearance of antibody at the site of introduction of antigen is due to local production of antibody or to a local accumulation of antibody.

Rabbits, injected intracutaneously with varying amounts of killed tubercle bacilli suspended in paraffin oil, were tuberculin-tested at seven-day intervals. At varying intervals these animals were sacrificed, and the areas of skin, axillary lymph nodes, spleen, liver, and lung were removed. After preparation, the supernatant fluids of these tissues were used for complement fixation titration.

Complement-fixing antibody was demonstrable in the blood serum in only one of eleven animals by the seventh day, and in four of eight animals by the fourteenth day. Antibody was detectable in the extracts of the skin lesions by the seventh day in most animals and was present in the lesions of all animals on and after the eleventh day. During the first three weeks, complement-fixing antibody in an extract prepared by suspending one part by weight of tissue from a local cutaneous site in five parts of physiologic saline and was generally detected in a concentration higher than that found in the blood. The titer of antibody at the injected cutaneous site tended to increase with the quantity of heat-killed tubercle bacilli injected into the skin up to a definable maximum. Extracts of spleen contained no antibody. Extracts of axillary node, lung, and liver contained antibody in minimal amounts in the presence of a high blood serum titer, and this was probably occasioned by residual blood serum in these tissues. The extracts of skin reactions produced by paraffin oil, old tuberculin, or cod-liver oil contained no demonstrable antibody or a very low titer.

Following the reinjection of killed tubercle bacilli suspended in paraffin oil into rabbits with antibody already present in the serum, complement-fixing antibody appeared no earlier in the cutaneous lesions than in normal rabbits.

From the above observations it is concluded that complement-fixing antibody is formed in the skin at the site of injection of killed tubercle bacilli suspended in paraffin oil.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Anaphylaxis in Serum Therapy. Kellett, C. E.: Practitioner **144:** 276, 1940.

The immunologic characteristics of serum shock and serum sickness are analyzed. The treatment and prevention of these two conditions are discussed.

Common Skin Diseases in Childhood. Klinke, K.: Med. Klin. **35:** 1208, 1939.

Telangiectasis, impetigo, furunculosis, seborrheic dermatitis, and infantile eczema are discussed. Avoidance of overnutrition, reduction of animal fat in the diet, and fluid restriction are recommended for the latter condition, together with elbow restraint and local ointments. The mother should be told that improvement, not cure, is the usual result, and that spontaneous improvement usually occurs at about 1½ years of age.

Incidence of Skin Eruption Among Infants and Preschool Children. Silvers, S., and Coe, M.: J. Pediat. **16:** 160, 1940.

In a numerical analysis of 1,700 children, half of whom were under 1 year of age, the authors report eczema the most frequent skin abnormality, with an incidence of 5 per cent. The incidence of seborrheic eczema was 2.5 per cent and that of papular urticaria with eczema a little over 1 per cent. The children were seen at two baby health stations in New York City. The group included under "infantile eczema" is extended in this report to include the age group from 2

to 6 years. What is probably the most common skin abnormality of infancy—a diaper and ammonia dermatitis—is mentioned in the text but is not listed in the frequency table.

Folliculitis with dermatitis of the face occurred exclusively in infancy and was the second most common abnormality. It appeared to be due to the use of soap and water in the majority of cases.

A Nasal and Systemic Upset of Possible Thymic Origin. Oaks, W., and Allen, W.: Eye, Ear, Nose, and Throat Monthly **18**: 231, 1939.

The occurrence of protracted coryza, dry skin, early teething, and an adult type of white blood differential count in infancy or childhood is often found in association with a family history of allergy. The oral administration of thymus gland is said to benefit the condition greatly.

Immunity: Clinical and Experimental Observations. Thelander, H. E.: California & West. Med. **52**: 64, 1940.

Some persons apparently have an immunity to diseases which the great majority does not share; other persons, despite a previous attack of a disease, such as measles, which usually confers immunity, acquire that disease a second time. In the same person there is considerable evidence that immunity changes spontaneously and is not a static affair. The great variability which can be expected in immune response as measured by one method is indicated by this report of sixteen adults and nineteen children. In these two groups the diphtheria antitoxin titer was determined after a given number of diphtheria toxoid injections. The children were unselected, and the adults were Schick-positive medical students. The children varied from 0.04 to 4 units per cubic centimeter of serum, and the adults from .004 to 3 units per cubic centimeter. Longitudinal studies on several persons show a tendency for a seasonal rise of antitoxin in the winter and spring. According to this study, the level at which the Schick test appeared to become negative was in the neighborhood of 0.01 or 0.005 unit per cubic centimeter of serum.

Studies in Immunity: Correlation of the Reaction to the Schick Test and the Diphtheria Antitoxin Content of the Blood Serum in Children With Scarlet Fever. Duffy, C. E., and Mitchell, A. G.: Am. J. Dis. Child. **59**: 479, 1940.

Of twenty-two children with scarlet fever, eight had a positive Schick test. In all eight there was less than 0.002 unit of diphtheria antitoxin per cubic centimeter of serum. With only two exceptions, all fourteen children with a negative Schick test had over 0.002 unit. The borderline of a negative Schick test then appeared to be 0.002 unit of antitoxin per cubic centimeter of serum. Since this agreed with reports on normal children, it was concluded that there is no increased sensitivity of the skin to diphtheria toxin in scarlet fever.

Familial Occurrence of Eosinophilia. Malmberg, N.: Acta paediat. **26**: 277, 1939.

It is customary to regard eosinophilia as due to some pathologic agent. Helminthiasis, allergy, malignancy, scarlet fever, and postinfectious and posttoxic states come to mind. Naegeli even states that eosinophilia always represents a reaction and cannot, therefore, be constitutional.

Nevertheless, the occurrence of a familial or constitutional eosinophilia is reported in which no demonstrable cause for the condition could be found. The mother had from 6 to 7 per cent eosinophilia; three sons had from 11 to 26 per

cent eosinophilia. On being checked six months later, all still showed eosinophilia, and at no time could any of the usual causes be found.

Thirteen instances of familial eosinophilia reported by other authors are mentioned.

Concerning a Case of Eczema Vaccinatum. Asperger, H.: Wien. klin. Wchnschr. **30**: 826, 1939.

A 12-year-old child was vaccinated successfully. He was permitted to play with a 9-month-old sister with eczema, who then developed a generalized vaccinia which had a fatal outcome. The 12-year-old child himself was febrile and confined to bed at the height of his vaccination. The mother also inoculated herself on the face despite previous successful vaccination, and she likewise had a severe case of localized vaccinia. The dangers of vaccinating siblings of children with eczema are pointed out.

Respiratory Revenge of Allergic Child. Tumpeer, I. H.: Illinois M. J. **77**: 37, 1940.

The author reviews the typical course of allergy in childhood. It is his belief that the family history is very important and that practically every allergic child has a positive family history. He considers that thymic enlargement, and, to a lesser extent, early pylorospasm, vomiting, respiratory abnormalities such as crowing and shallow breathing, cradle cap, craniotabes at 4 months of age, and rapid weight gain are all suggestive of allergy in the infant. He feels the presence of allergy is adequate cause, later on, for certain behavior deviations and admits that nothing would give him greater pleasure than subjecting an asthmatic analyst to analysis for relief of his asthma.

He expects the allergic person to react excessively to infections and to have a secondary sinusitis if he has nasal allergy. Surgery is warned against if the allergy is not attended to first.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Borderline Allergy. Its Relation to Hyperplastic Disease of the Respiratory Tract. Fox, N., Harned, J. W., and Peluse, S.: Arch Otolaryng. **31**: 502, 1940.

Fox, Harned, and Peluse call attention to certain types of borderline allergy of the upper respiratory tract and their relation to hyperplastic changes in tissues in these structures. They point out that the difficulties in proper evaluation of the symptoms and pathologic changes of hyperplastic disease of the respiratory tract result in the classification of these borderline conditions under diseases in no way related to allergy. They further state that neither the texture nor the color of the tissues nor the character of the exudate gives any hint of the allergic nature of the borderline condition, since pallor, edema, and eosinophilia are not always present. They base the diagnosis of borderline allergy upon the finding of gross hyperplastic changes in a person with a history of allergy or in whose family there is a history of allergy and in whom a foreign protein study reveals positive sensitivity to particular allergens. Among the various hyperplastic conditions are

listed: chronic intermittent nasal obstruction; chronic lymphoid pharyngitis; frequent colds; recurrent acute laryngitis, pachydermia laryngis, singers' nodes, and papillomas; chronic purulent discharge, and tubal-tympanic catarrh.

Our observations are in agreement with those of Fox and his co-workers in that cases of borderline or subclinical allergy, particularly of the nose and sinuses, are frequently overlooked because of the lack of the typical edematous changes and because of the vagueness of the symptoms. We have encountered a definite group of cases in which stuffiness and sometimes dryness of the mucosa with postnasal discharge are the predominating symptoms. Often there is little or no sneezing. Eosinophiles are almost always present, but these are difficult to demonstrate because of the scanty amount of secretion available for observation. Repeated cytologic observations are therefore necessary before the diagnostic eosinophilia can be demonstrated. These patients are often subected to submucous resection or cauterization of the turbinates without relief. Most of the cases of this type are caused by inhalants, particularly house dust. The symptoms are usually more pronounced in the winter than in the summer. Cases of this type are sufficiently common to warrant careful consideration from the rhinologic standpoint. With proper allergic management, most satisfactory results should be obtained.

Sinusitis in Allergic Persons. Scholz, W.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **45**: 14, 1939.

Scholz discusses the part played by polyps in sinusitis, and he believes that they are usually of allergic origin. He advises radical surgical interference. When satisfactory results are not obtained, he advises detailed study of nasal secretions and blood smears for eosinophilia and allergic study. He advises such nonspecific treatment as the use of splenic extract and the administration of calcium and phosphorus. He also recommends cauterization of the turbinates with trichloroacetic acid. These observations are characteristic of the general prevailing attitude of rhinologists on the management of cases with polyposis, in that surgical procedures should be instituted first. We have found that far better results are obtained by instituting allergic management first, and then performing whatever surgical procedures are necessary, usually employing the more conservative types of operations.

Of What Value Is Roentgen Therapy for Sinusitis? Gatewood, E. T.: Arch. Otolaryng. **31**: 275, 1940.

The question of the value of roentgen therapy for sinusitis is presented by Gatewood, whose observations are based upon a study of twenty-two cases of chronic sinusitis. He feels that roentgen therapy for any form of sinusitis is in its earliest experimental stage. The twenty-two patients were examined roentgenologically and rhinologically before and after receiving therapy, with no definite evidence of uniform improvement of the infection despite roentgenologic changes. It is further stated that, with the exception of a single case, microscopic examination of the polypoid content of eight antra which had been subjected to roentgen therapy did not show any obvious difference from similar pathologic content of other antra which had not received like treatment.

Edema of the Larynx. A Study of the Loose Areolar Tissues of the Larynx. Miller, M. V.: Arch. Otolaryng. **31**: 256, 1940.

The subject of edema of the larynx, with a study of the loose areolar tissues, is presented in a very interesting manner by Miller. This presentation considers the

history of previous observations, the physiologic nature of edema, the symptoms caused, and the treatment. The subject of angioneurotic edema of the larynx is discussed in considerable detail. In the treatment of these cases, the hypodermic administration of 1:1,000 epinephrine and the local application of 1:100 epinephrine are suggested. Scarification and application of medication by means of swabs are unwise. The patient should be constantly watched, and facilities should always be on hand for quick tracheotomy. The mechanism of edema of the larynx was studied by means of experiments on the cadaver. From these observations it was concluded that a dense and fibrous band holds down the mucosa along the midline over the cricoid cartilage on its esophageal surface, running in a vertical direction. Submucous areolar tissue on the base of the tongue extends upward as high as the tip of the epiglottis. Attention was called to the fact that certain types of edematous fluid may spread more rapidly than others because the protein content affects the diffusibility. Various factors such as these make it difficult to evaluate clearly the clinical importance of these particular findings. Localized edema is known to occur, however, in various parts of the larynx in areas which might be limited by the barriers described.

Allergic Vertigo. Criep, L. H.: Pennsylvania M. J. 43: 258, 1939.

Criep discusses the subject of vertigo of allergic origin, stating that it is caused by edema of the various structures of the internal ear. The symptoms produced depend upon the particular structure involved. The most common complaints listed were tinnitis, deafness, and gastric disturbances. The deafness is usually of a transitory nature. The differential diagnosis is based upon family history of allergy, personal history of allergy, blood eosinophilia, skin tests, response to adrenalin, and the absence of other etiological factors. Allergic management with particular attention to the diet is often beneficial.

Correspondence

The Editor,

THE JOURNAL OF ALLERGY.

I would like to call attention to the use of glycerin, 50 per cent, to slow absorption of epinephrine.

The introduction of slow epinephrine in peanut oil by Keeney gave us a valuable addition to our remedies in the treatment of severe asthma.

Glycerin, however, is a better vehicle for epinephrine because it is harmless to the body economy, is self-sterilizing, maintains the potency of materials dissolved in it, and is slowly absorbed. Preparations of epinephrine in 50 per cent glycerin are easily made, either from the dry epinephrine or the 1:100 solution.

We have found that a 1:300 extract gives the best results in dosage of from 0.2 to 0.3 c.c. Sterilization is by Seitz filtration.

We suggest its more frequent use.

AARON BROWN, M.D.
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New York, N. Y.

March 29, 1940.